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LaCeS2: A multicentre, randomised controlled trial of Laparoscopic versus Open Colorectal Surgery in the Acute Setting

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Health Technology Assessment Programme (Grant Ref: NIHR128815)

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Randomise participants using the 24 hour randomisation system

Web: https://lictr.leeds.ac.uk/webrand/ **Or Tel: 0113 343 2290**

Please ensure the Eligibility Checklist and Randomisation CRF are completed before phoning the randomisation line / accessing the web randomisation

NB: Access codes will be required.

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2 CONTENTS

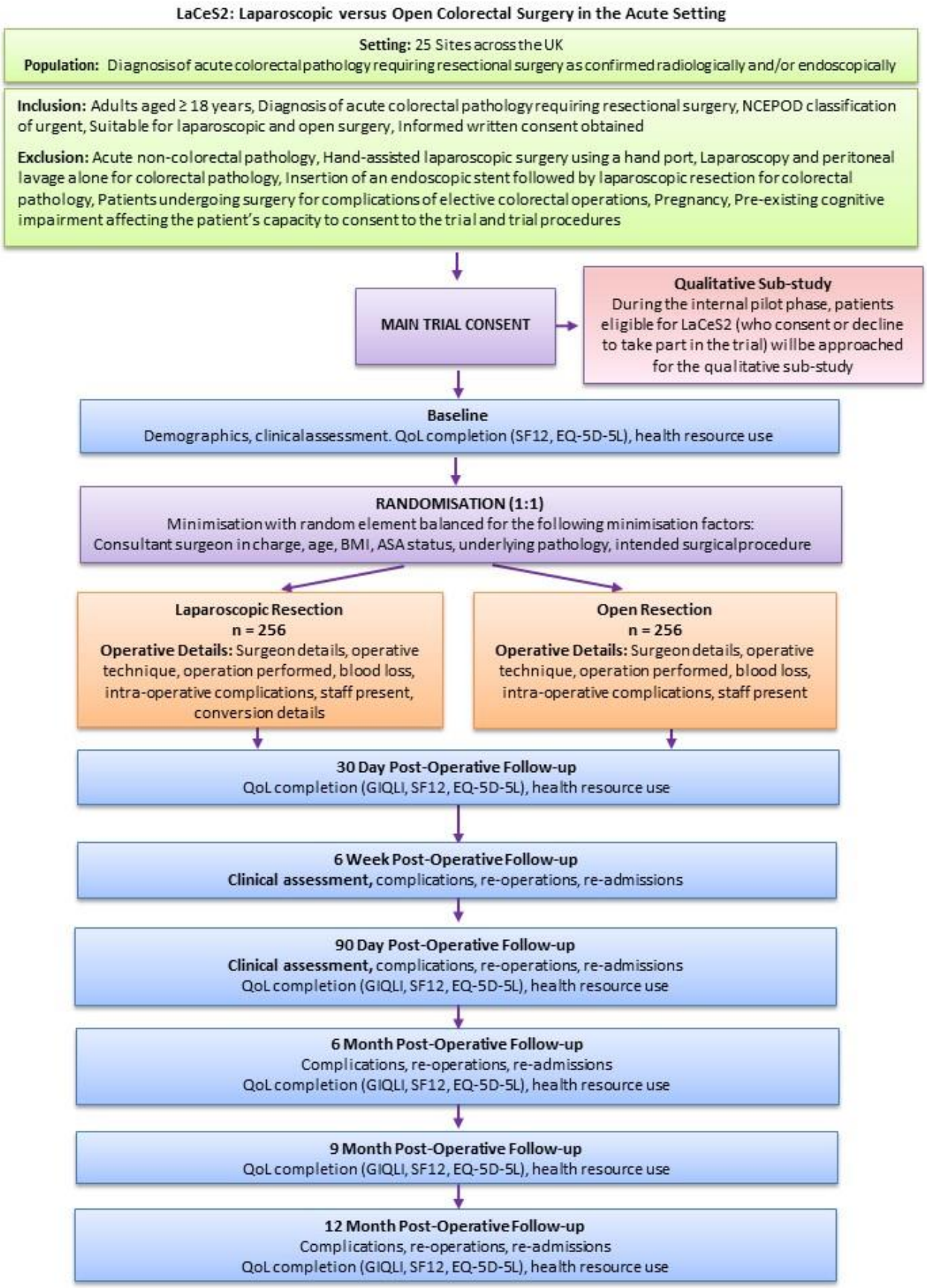
3 TRIAL SUMMARY

Trial Title	A multicentre, randomised controlled trial of Laparoscopic versus Open Colorectal Surgery in the Acute Setting
Trial Acronym	LaCeS2 Trial
Trial Background	Emergency general surgery is one of the commonest reasons for admission to hospital. A wide range of problems can lead to an emergency admission, with diseases that affect the large bowel making up a third of diseases that present as an emergency. There is substantial evidence demonstrating the benefits of laparoscopic colorectal surgery in the elective setting, with little equivalent evidence regarding its use in the acute setting. Patients requiring emergency surgery present with different physiology, varying degrees of sepsis & advanced disease that has the potential to make laparoscopic surgery more technically challenging. The evidence from the elective setting cannot readily be translated to this acute setting. It is therefore imperative to evaluate the role of laparoscopic surgery specifically in the acute setting in order to provide an evidence base to aid clinical decision making.
Trial Design	A phase III, multicentre, randomised controlled superiority trial investigating the effectiveness and cost-effectiveness of laparoscopic colorectal emergency surgery compared to open surgery. An internal pilot phase will assess recruitment feasibility and an integrated qualitative study will assess broader site implementation of trial-related procedures, better understand equipoise and identify any further barriers to recruitment.
Outcome measures	**Primary outcome measure:** • Incidence of 30 day post-operative complications defined as the number of patients with a complication (of any grade) occurring within 30 days of surgery as a proportion of all randomised patients **Key secondary outcome measure:**

	• Quality of life (GIQLI and SF-12®) over 12 months post-operation **Secondary outcome measures:** • Severity of 30 day post-operative complications • Incidence of 90 day post-operative complications and incidence of surgery-specific complications over 12 months post-operation • Incidence and severity of intra-operative complications and incidence of conversions from laparoscopic to open surgery • 30 day post-operative: mortality, re-operations and re-admissions • Time to restoration of gastrointestinal function • Length of post-operative hospital stay • Cost-effectiveness
Trial Population:	512 participants, aged ≥ 18 years, with a radiological and/or endoscopic diagnosis of acute colorectal pathology requiring resectional surgery. Participants will have an NCEPOD classification of 'urgent', subdivided into NELA categories 2a (approx. 2-6 hours of decision to operate) or 2b (approx. 6-18 hours of decision to operate) and be suitable and willing to receive laparoscopic or open surgery.
Randomisation	Randomisation (1:1) to receive either laparoscopic or open surgery. Randomisation to be performed by the Clinical Trials Research Unit (CTRU), Leeds.
Trial Intervention:	The intervention being assessed in this trial is the use of laparoscopic surgery in the unplanned, acute setting. This involves the use of multiple small incisions to enable the introduction of instruments to be able to undertake the operation. The comparator is open surgery which is carried out through a large midline incision.
Duration:	All participants will be followed up to 12 months post-operation.
Evaluation of outcome measures	Participants will be assessed at 6 weeks, 90 days, 6 months, and 12 months post-operatively.

	Quality of Life (QoL) and patient-reported outcomes (assessed using the GIQLI, EQ-5D-5L™ and SF-12® questionnaires) and health resource use will be measured at 30 days, 90 days, 6 months, 9 months and 12 months post-operatively. Complications will be documented during trial treatment and follow-up.

4 TRIAL SCHEMA



5 BACKGROUND

The National Emergency Laparotomy Audit (NELA) in the UK reports that approximately 30,000 patients undergo major emergency gastrointestinal surgery per annum, of which a third undergo surgery for colorectal pathology [1]. The management of emergency colorectal pathology can be challenging due to the range of presenting pathology including colorectal cancer, inflammatory bowel disease and diverticular disease, combined with variable patient physiology, associated sepsis and potentially advanced disease. Emergency colorectal surgery is associated with significant morbidity and mortality, with reported rates of 33-71 and 14-17 per cent respectively [2, 3]. This has a significant burden on patients with prolonged recovery and an adverse impact on overall quality of life (QoL).

5.1 EXISTING RESEARCH

There are some emerging reports that performing laparoscopic surgery in the emergency setting for colorectal pathology may improve clinical outcomes. Three systematic reviews collating evidence from a range of single-centre, retrospective case series and cohort studies reported reduced length of stay and post-operative morbidity in patients undergoing emergency laparoscopic surgery [4-6]. All three reviews identified significant methodological weakness including selection, reporting and outcome bias. The collective conclusion was that the available data were not robust enough to definitively inform the role of emergency laparoscopic colorectal surgery. This lack of high quality evidence is reflected in the lack of uptake in emergency laparoscopic surgery, with NELA reporting static rates of emergency laparoscopic surgery of ~15% between 2014 and 2018 [1]. Robust, high quality data from a large scale, definitive clinical trial is required to inform the implementation of laparoscopic surgery in the emergency setting.

Clinical trials in the emergency surgical setting are complex due to the competing priorities of delivering definitive and time-sensitive clinical care and implementing trial-related processes such as recruitment, consent, randomisation and blinding. A number of surgical trials in the emergency colorectal setting have closed early due to poor recruitment rates [7, 8] or a higher incidence of adverse events than anticipated [9].

5.1.1 LaCeS FEASIBILITY TRIAL

The LaCeS feasibility trial was undertaken to determine the feasibility, acceptability and safety of conducting a trial of laparoscopic versus open colorectal resection in the acute setting [10]. The LaCeS trial was undertaken across 5 NHS centres across the UK and was successfully

completed on time and to target in November 2017 [11]. LaCeS successfully achieved its primary endpoints; including:

Recruitment : During the recruitment period 564 patients were identified as undergoing an emergency colorectal resection across all sites using the NELA dataset. A total of 119 patients were screened within the trial and were assessed for eligibility, of which 94 (79.0%) patients were considered eligible and 72 (76.6%) patients consented to participate in the trial. The average steady state recruitment rate was 1.2 patients/month/site overall, with observed centre variation of 0.57 – 2.78 patients per month. The overall mean steady-state recruitment rate was 0·9 patients per month per site when the lead site assumed the rate of the next highest recruiting site.

Safety: Overall, the safety data obtained for laparoscopic emergency colorectal surgery indicated an acceptable safety profile. The safety of laparoscopic emergency colorectal surgery was assessed by measuring the incidence of intra-operative and post-operative complications and mortality rates. Patient safety indicators (PSIs), as defined by the Agency for Healthcare Research and Quality, were also collected. LaCeS reported an incidence of recorded intra-operative complications of 3%, the incidence of 30-day post-operative complications was 27.3% and the incidence of patient safety indicators was 12.1% in the laparoscopic arm. In addition, 39.4% of patients in the laparoscopic arm converted to open surgery.

Acceptability and Feasibility: Baseline compliance for clinical data was 99.8% and for health related quality of life (HrQoL) data was 93.8%. Overall compliance for all follow up was 94.6% for clinical data and 82.0% for HrQoL data. The Bang Blinding Index was 0.21 (95% CI 0.14 – 0.27) in the laparoscopic arm and 0.53 (95% CI 0.48 – 0.59) in the open arm which means there was a failure to adequately blind patients to treatment allocation in both groups. Patients preferred to be told of their treatment allocation in the immediate post-operative period. The majority of the trial processes were acceptable to patients and healthcare professionals. The follow up schedule was felt to be intensive due to the number of clinical visits required.

5.2 RATIONALE FOR LaCeS2

The results from the LaCeS feasibility trial have provided sufficient methodological evidence regarding trial design, delivery and justification for a large-scale, definitive, Phase III trial. LaCeS2 has been designed as a multicentre, randomised controlled superiority trial with an internal pilot and embedded qualitative study to compare laparoscopic and open emergency

colorectal resection. LaCeS2 will provide definitive data on the effectiveness and cost-effectiveness of emergency laparoscopic colorectal surgery in comparison to open surgery.

6 AIMS AND OBJECTIVES

The aim of this trial is to provide definitive evidence for the role of laparoscopic colorectal surgery in the emergency setting. LaCeS2 will test the hypothesis that laparoscopic surgery is superior to the standard care of open surgery within adult patients undergoing emergency colorectal surgery, in terms of post-operative clinical and cost-effectiveness.

6.1 PRIMARY OBJECTIVE

To determine if laparoscopic surgery in the emergency colorectal setting reduces the incidence of 30-day post-operative complications when compared to the standard care of open surgery.

6.2 KEY SECONDARY OBJECTIVE

To examine and report, in terms of laparoscopic versus open colorectal surgery:

1) Patient-reported Quality of Life within 12 months post-surgery

6.3 SECONDARY OBJECTIVES

To examine and report, in terms of laparoscopic versus open colorectal surgery:

2) Severity of 30 day post-operative complications
3) 90 day post-operative complications and surgery specific complications over 12 months post operatively
4) Intra-operative complications and conversions from laparoscopic to open surgery
5) 30 day post-operative: patient mortality, re-operations and readmissions
6) Restoration of gastrointestinal function
7) Length of post-operative hospital stay
8) Cost-effectiveness

7 DESIGN

7.1 TRIAL DESIGN

LaCeS2 is a phase III prospective, multicentre, pragmatic, unblinded, two-arm individually randomised controlled superiority trial, investigating the clinical effectiveness and cost-effectiveness of laparoscopic colorectal emergency surgery compared to open surgery. The trial includes a 12-month internal pilot phase (Section 7.2) and embedded qualitative study (Section 22). Recruitment will be conducted within acute general surgery services.

A total of 512 adult, consenting patients requiring emergency colorectal surgery will be randomised over 3 years on a 1:1 basis between laparoscopic and open surgery using minimisation (incorporating a random element).

All participants will be followed up for a period of 12 months post-operatively, providing clinical and patient-reported outcomes. The trial will not be blinded to participants, medical or trial staff for pragmatic reasons, based on the results of the feasibility study.

7.2 INTERNAL PILOT PHASE

The trial will include a 12 month internal pilot phase, occurring within the first 12 months of open recruitment. The aim of the internal pilot phase is to confirm that the opening of sites and recruitment on a larger scale is feasible.

An independent Data Monitoring and Ethics Committee (DMEC) will meet and report to the independent Trial Steering Committee (TSC) at the end of the pilot phase, which will subsequently report its recommendations including trial continuation to the funder. Progression considerations will be based on review of: i) recruitment, ii) safety, iii) qualitative evaluations.

8 ELIGIBILITY

8.1 RESEARCH SITE ELIGIBILITY

The trial will open in at least 25 NHS research sites across the UK. Each site must fulfil a set of pre-specified criteria and complete a registration form which verifies that the research site is willing and able to comply with the trial requirements. This will be signed by the proposed local Principal Investigator (PI) on behalf of all staff who will be affiliated with the trial. Research sites will be required to obtain local management approval, return all required essential documentation to CTRU and undertake a site initiation with the CTRU prior to the start of

recruitment into the trial. An emergency-trial specific training package developed by the qualitative research team will also be provided to sites at baseline (during set-up) and on an ongoing basis throughout recruitment (see section 23.3 for further details).

Participation of research sites will be dependent upon the following criteria:

- Has dedicated emergency surgery services with appropriate provisions for emergency laparoscopic surgery
- Has dedicated elective laparoscopic colorectal surgery services
- Anticipating to recruit at least 8 - 12 participants per year

8.2 SURGEON ELIGIBILITY

Prior to randomising participants, all participating consultant surgeons must have performed a minimum of 50 laparoscopic colorectal resections and must perform at least 20 laparoscopic resections a year, with equivalent experience in open surgery (this can include procedures in both the emergency and elective setting). The number of resections per year are in line with the ACPGBI guidance [12] outlining requirements regarding minimum number of annual colorectal resections undertaken by colorectal surgeons.

The participating consultant surgeon will be responsible overall for the patient and will provide appropriate supervision for surgical registrars.

Surgeon experience level - the total number of (elective and emergency) laparoscopic resections and open surgeries that each participating consultant surgeon has performed – will be collected at the point of trial entry, and will continue to be collected on an ongoing basis throughout the trial (this will also include relevant experience gained outside of the trial).

The trial will be registered with the NIHR Associate PI Scheme. Associate PIs must be able to contribute to the trial for at least 6 months. Please contact the CTRU to discuss the inclusion of Associate PIs at sites.

8.3 PATIENT ELIGIBILITY

Eligibility waivers to the inclusion or exclusion criteria are not permitted and participants must not be randomised more than once into the LaCeS2 trial.

8.3.1 INCLUSION CRITERIA

1. Aged ≥18 years
2. Diagnosis of acute colorectal pathology requiring resectional surgery (for example; acute diverticular disease, inflammatory bowel disease, large bowel obstruction and colonic perforation) confirmed radiologically and/or endoscopically. A colorectal resection will be defined as surgery from the caecum to the anus.
3. Urgency of operation defined as per NCEPOD guidelines as urgent.
   - Urgent - Intervention for acute onset or clinical deterioration of potentially life-threatening conditions, for those conditions that may threaten the survival of limb or organ, for fixation of many fractures and for relief of pain or other distressing symptoms. Normally within hours of decision to operate, subdivided into NELA categories of 2a (approx. 2-6 hours) or 2b (approx. 6-18 hours).
4. Suitable for laparoscopic and open surgery
5. Informed written consent obtained
6. Able and willing to comply with the terms of the protocol including QoL questionnaires

8.3.2 EXCLUSION CRITERIA

1. Acute non-colorectal pathology (for example; adhesional small bowel obstruction, appendicitis, peptic ulcer disease)
2. Hand-assisted laparoscopic surgery using a hand port
3. Laparoscopy and peritoneal lavage alone for colorectal pathology
4. Insertion of an endoscopic stent followed by laparoscopic resection for obstructing colorectal pathology
5. Patients undergoing emergency surgery for complications of elective colorectal operations
6. Pregnancy[1]
7. Pre-existing cognitive impairment affecting the patient's capacity to consent.

[1] It is the local surgeon's responsibility to ensure this is assessed in people of child-bearing potential according to local standard of care

8.3.3 CONCURRENT CLINICAL TRIALS

Eligibility for co-enrolment in any other clinical trials will be assessed on a trial-by-trial basis by the LaCeS2 trial team at the Clinical Trials Research Unit (CTRU) at the University of Leeds. For any queries regarding co-enrolment, please contact the CTRU trial team (ctru-laces@leeds.ac.uk).

9 RECRUITMENT PROCESS

9.1 RECRUITMENT SETTING

Participants will be recruited from at least 25 NHS sites across the UK (including both university teaching hospitals and district general hospitals). Patients will be identified within the emergency general surgical framework at participating centres. A total of 512 participants (256 in each arm) will be recruited into the trial over a 36 month recruitment period.

9.2 ELIGIBILITY SCREENING

All patients with suspected acute colorectal pathology will be assessed radiologically and/or endoscopically, as part of routine care prior to being considered/approached for the trial. Participating research sites will be required to complete a log of all patients screened for eligibility who are not randomised either because they are ineligible or because they decline participation. Anonymised information will be collected including:

- Age
- Sex
- Date screened
- Disease characteristics
- Reason not eligible for trial participation, or
- Eligible but declined and reason for this, or
- Other reason for non-randomisation

This information will be requested from research sites on a regular basis (at least 3 monthly) by the CTRU. Documented reasons for ineligibility or declining participation will be closely monitored by the CTRU as part of a regular review of recruitment progress.

9.3 APPROACH FOR PARTICIPATION

Following clinical **and** radiological/endoscopic diagnosis, suitability for inclusion into the trial will be assessed according to the eligibility criteria (see section 8) and patients will be approached for possible recruitment. Patients may be approached for the trial at any time of

day, providing that the timing of approach is considered appropriate by the local research team.

9.3.1 WRITTEN INFORMED CONSENT

A verbal explanation of the trial along with the approved Participant Information Sheet (PIS) will be provided by a suitably qualified member of the healthcare team for the patient to consider. The PIS will provide detailed information about the rationale, design and personal implications of the study. A PIS Supplementary Information Document, containing additional information about the trial, will also be made available to the patient by a member of the local research team if the patient expresses an interest in reading this document (this document is referenced in the main trial PIS). Reading the Supplementary Information Sheet is optional for patients and they do not need to read this document in order to consent to the LaCeS2 trial, if they do not wish to do so.

Following information provision, patients must be given the opportunity to discuss the trial with their family and medically qualified members of the healthcare team before they are asked whether they would be willing to take part in the trial.

Given the emergency nature of the LaCeS2 trial the time available to consider participation will be shorter than in the elective setting. Patients will be given as long as they need to consider participation into the trial (within the time available prior to surgery). Ideally this will be at least 2 hours. The right of the patient to refuse consent without giving reasons will be respected.

Patients who wish to participate will be invited to provide written informed consent including explicit consent for the transfer of a copy of their signed consent form to the CTRU. Following consent patients will be formally assessed for eligibility.

Informed consent may only be obtained by the PI or an appropriate, delegated, healthcare professional. The healthcare professional must have knowledge of the trial interventions and have received training in the principles of GCP and the Declaration of Helsinki 1996. The healthcare professional must be fully trained in the trial according to the ethically approved protocol and be authorised and approved by the PI to take informed consent as documented in the trial APL. The PI retains overall responsibility for the informed consent of participants at their research site.

The participant consent form with all original signatures must be retained in the Investigator Site File (ISF). A copy of the signed consent form must be given to the participant, and a record of the consent process, detailing the date of consent and witnesses, must also be kept in the participant's medical notes (this may include a copy of the consent form as per local practice). A copy of the signed consent form must also be transferred to the CTRU.

Participants will remain free to withdraw from the trial at any time by revoking consent without giving reasons and without prejudicing any further treatment.

9.3.2 PATIENT INTERVIEWS

During the internal pilot phase, patients who are approached for the trial, both decliners and consenters, will be invited to take part in a brief interview to find out their views about the trial recruitment processes. Patients will be approached when considered well enough by their clinician. Patients will be invited to take part in a qualitative sub-study involving a face-to-face, telephone or video chat interview to explore their views about the trial recruitment materials and processes, and for decliners we will also seek to understand their reasons for declining to take part in the trial. The initial approach regarding this sub-study will generally take place at any point prior to discharge, once their clinical team feels this is appropriate. In instances where no initial approach was made e.g. owing to concerns around causing the patient additional distress, the patient will be approached at point of discharge or by post/telephone when they return home. For details of the sub-study refer to section 22.

9.3.3. LOSS OF CAPACITY FOLLOWING INFORMED CONSENT

Loss of mental capacity of a participant after giving informed consent for the trial is expected to be a rare occurrence. Should this eventuality occur, this should be reported to CTRU via the Withdrawal eCRF with no further trial procedures or data collection occurring from this point. Any data collected up to the point of withdrawal will be kept on record and used in the trial analysis. Further details regarding participant withdrawal can be found in section 10.5

9.4 RANDOMISATION

Informed written consent for entry into the trial must be obtained prior to randomisation (see section 9.3).

9.4.1 TIMING OF RANDOMISATION

Randomisation should take place as soon as possible after informed consent has been obtained and eligibility confirmed, including the anaesthetist assessment.

9.4.2. RANDOMISATION PROCESS

Following confirmation of written informed consent and eligibility, patients will be randomised into the trial by an authorised member of staff at the trial site. Participant-completed baseline questionnaires (SF-12®, EQ-5D-5L™ and a Health Economics Questionnaire, see section 11.5) should be completed after consent has been obtained and prior to randomisation, however, where this is not possible these must be completed before the participant is informed of their randomised treatment allocation.

Randomisation will be performed centrally using the CTRU automated 24-hour randomisation system which can be accessed via the web or telephone. User ID codes and personal identification numbers (PINs), provided by the CTRU, will be required to access the randomisation system.

The following information will be required at randomisation:

- Patient details, including initials, date of birth, height and weight
- Name and code of the research site
- Name of the person making the randomisation
- Confirmation of eligibility
- Confirmation of written informed consent
- Minimisation factors (see section 9.4.3)

The randomisation system will allocate participants a unique 5 digit trial number and inform of the randomised operation for that participant (laparoscopic or open surgery).

24 HOUR RANDOMISATION

Web https://lictr.leeds.ac.uk/webrand/ or Tel: 0113 343 2290

Please ensure that informed consent has been taken and eligibility is confirmed prior to phoning the randomisation line / accessing the web randomisation

NB: Access codes will be required.

Immediately after randomisation, please send the Consent Form and Contact Form to CTRU via fax or secure file transfer

Fax: 0113 343 6774

9.4.3 TREATMENT ALLOCATION

Participants will be randomised on a 1:1 basis to receive either laparoscopic or open surgery and will be allocated a unique trial number. Randomisation will be based on a minimisation algorithm with random component ensuring that treatment groups will be balanced for the following minimisation factors:

- Intended Consultant Surgeon in charge
- Patient age
    - 18-<50
    - 50-59
    - 60-69
    - 70-79
    - ≥ 80
- Body Mass Index (kg/m^2)
    - <25 kg/m^2
    - 25-<30 kg/m^2
    - ≥30 kg/m^2
- ASA status
    - I or II - A normal healthy patient or A patient with mild systemic disease.
    - III - A patient with severe systemic disease.
    - IV Or V - A patient with severe systemic disease that is a constant threat to life or A moribund patient who is not expected to survive without the operation.
- Nature of underlying colorectal pathology
    - Benign
    - Malignant
    - Unsure
- Nature of intended surgical procedure
    - Segmental colectomy, Right hemicolectomy, Left Hemicolectomy or Sigmoid Colectomy
    - Hartmann's procedure
    - Subtotal colectomy
    - Other

10 INTERVENTION DETAILS

10.1 SCHEDULE OF CLINICAL ASSESSMENTS/DATA COLLECTION POINTS

The timing of clinical assessments and data collections points are summarised in Table 1. All participants will be followed up until 12 months post-operation.

Table 1 Schedule of events

	Events	Pre-trial diagnostics	Baseline/ pre-op	Surgery	Hospital discharge	30 days post-op *(QoL only)*	6 weeks post-op[2]	90 days post-op[3]	6 months post-op *(no clinic visit - data from medical notes)*	9 months post-op *(QoL only)*	12 months post-op *(no clinic visit - data from medical notes)*
Clinical assessments/ investigations	**Radiological/endoscopic diagnosis[4]**	**√**									
	Clinical examination		**√**				**√**	**√**			
	Trial consent		**√**								
	Operative details			**√**							
	Complications			**√**			**√**	**√**	**√**		**√**
	Re-operations/re-admissions						**√**	**√**	**√**		**√**
Data collection time points	**Eligibility CRF**		**√**								
	Baseline CRF		**√**								
	Operative CRF			**√**							
	Discharge CRF				**√**						
	Post-operative f/up CRF						**√**	**√**	**√**		**√**
Participant completed questionnaires	**GIQLI**					**√**		**√**	**√**	**√**	**√**
	SF-12®		**√**			**√**		**√**	**√**	**√**	**√**
	EQ-5D-5L™		**√**			**√**		**√**	**√**	**√**	**√**
	Health Resource Use		**√**			**√**		**√**	**√**	**√**	**√**

[2] It is permissible for this visit to be conducted via telephone if it is not possible to see the participant in clinic
[3] It is permissible for this visit to be conducted via telephone if it is not possible to see the participant in clinic
[4] As part of standard clinical practice

10.2 PRE-OPERATIVE INVESTIGATIONS AND PREPARATION

Pre-operative investigation and treatment will be as per institutional protocol and must include radiological imaging i.e. CT or MRI scan and/or endoscopy.

10.3 SURGERY

Conventional laparoscopic and open surgery should be undertaken in keeping with standard practice and overseen/performed by the randomising surgeon, the only difference is the operative approach. The specifics of each operation will be at the discretion of the operating surgeon, as will the decision to convert to an open operation.

Laparoscopic surgery includes the use of multi-port or single-port incisions to establish pneumoperitoneum to enable resection. Conversion to an open operation will be defined as the use of a midline laparotomy wound for any part of the colorectal dissection. The use of a limited laparotomy wound to facilitate specimen extraction is permissible.

10.4 POST-OPERATIVE CARE

Post-operative care will be as per institutional protocol. Participants will be followed up for 12 months post-operatively for trial purposes. Clinical, patient-reported outcome and health economic data will be collected at baseline, 30 days (patient-reported), 6 weeks, 90 days, 6 months, 9 months (patient-reported) and 12 months post-operatively.

10.5 PARTICIPANT WITHDRAWAL

In line with usual clinical care, cessation or alteration of treatment at any time will be at the discretion of the attending clinician or the participant themselves.

In the event that a participant withdraws prior to randomisation, no further data is required to be submitted. In the event that a participant withdraws after randomisation (prior to, or after their operation) participants will still attend follow-up visits unless unwilling to do so and safety data and follow-up data will continue to be collected.

If a participant explicitly states that they do not wish to contribute further data to the trial or to complete any further participant questionnaires, the CTRU must be informed via the Withdrawal eCRF on the LaCeS2 database.

The PI or delegate must make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial are defined and documented using the **Withdrawal eCRF within 7 days** of the withdrawal request in order

that the correct processes are followed by the CTRU and research site following the withdrawal of consent.

11 DATA COLLECTION

Participating research sites will be expected to maintain a file of essential trial documentation (ISF), which will be provided by the CTRU, and keep copies of all completed CRFs for the trial. Paper CRFs, eCRFs and participant-completed questionnaires will contain the participant's unique trial number, date of birth, and initials. Clinical data will be collected at baseline, operation, hospital discharge and at 6 weeks, 90 days, 6 months and 12 months post-operation; participant-completed data will be collected at baseline and at 30 days, 90 days, 6 months, 9 months and 12 months post-operation.

11.1 SUBMISSION OF TRIAL DATA

Informed Consent Documents, Contact Details forms and Serious Complication data (SCs/USCs) requiring expedited reporting (see section 12.3.1) will be collected via paper case report forms (CRFs). Baseline participant-completed questionnaires will be collected on paper, and follow-up participant-completed questionnaires will be collected either on paper or electronically via patient-reported outcome software, dependent on participant choice. All other data collection will be via Remote Data Entry (RDE) on electronic case report forms (eCRFs) managed by the CTRU at the University of Leeds. Access to the live LaCeS2 database will be provided by the CTRU following sites being authorised to open to recruitment. An SSOP will offer guidance on RDE and completing the eCRFs. Missing and discrepant data will be flagged and additional data validations raised as appropriate by the CTRU data management team.

Data collected on paper CRFs (Consent, Contact details, SCs and USCs) will be sent to the CTRU, usually via standard post but in some cases by fax, email or secure electronic transfer. If Informed Consent Documents are posted to CTRU, they must be sent in a separate envelope to participant questionnaires.

Data must only be completed by personnel authorised to do so by the PI, as recorded on the trial-specific Authorised Personnel Log.

11.2 PRE-TREATMENT DATA COLLECTION

Participants must be screened, assessed for eligibility and have provided written informed consent before they can then be randomised (Section 9.4)

Data will be entered onto pre-operative eCRFs on the LaCeS2 database (Eligibility Checklist, Baseline and Randomisation Forms) and will include (but will not be limited to):

- Personal details and demographics including height, weight and sex
- Date of diagnosis
- Diagnosis at baseline
- Nature of intended surgical procedure
- Confirmation of eligibility
- Confirmation of written informed consent
- Minimisation factors (see section 9.4.3)
- Concomitant diseases/co-morbidities
- Details of previous abdominal operations

Following written informed consent, and wherever possible prior to randomisation (where this is not possible this must be prior to the participant being made aware of their randomised treatment), participants will also be asked to complete the baseline participant-completed questionnaires:

- SF-12®
- EQ-5D-5L™
- Health Resource Use

11.3 OPERATIVE DATA COLLECTION

Operative data will be entered into the Operative eCRF on the LaCeS2 database and will collate data relating to the surgical operation including (but not limited to):

- Consultant surgeon in charge
- Grade of operating surgeon
- Operative approach
- Type of operation performed
- Duration of operation
- Estimated blood loss
- Whether conversion to open surgery occurred, details and reason (laparoscopic arm only)
- Any intra-operative complications
- Staff present
- Intraoperative analgesic regime
- Operative findings

11.4 FOLLOW-UP DATA COLLECTION

11.4.1 DISCHARGE DETAILS

Hospital discharge details will be entered onto the Discharge eCRF in the LaCeS2 database at the point at which participants are discharged from hospital. Data collected will include (but will not be limited to):

- Date of discharge
- Date of restoration of gastrointestinal function, if applicable

11.4.2 REOPERATIONS

If the participant undergoes any further abdominal operations within 6 weeks of their index emergency operation, please complete the Re-operative eCRF.

11.4.3 DATA COLLECTION FOR CLINICAL ASSESSMENTS

Post-operative care will be as per institutional protocol. However, a clinical assessment must be carried out for all participants at 6 weeks and 90 days post-operation. The 6-month and 12-month post-operative assessment can be completed from participants' medical notes; participants do not need to be seen in clinic for trial purposes at these time points. Data collected during follow-up will include (but will not be limited to):

- Participant status (dead/alive)
- Complications
- Readmissions
- Reoperations (see section 11.4.2 for additional details)
- Details of further abdominal surgeries

At the post-operative reviews participants will be asked to complete the participant questionnaire booklets; for details of questionnaires completed at each post-operative review refer to section 11.5.

11.5 PARTICIPANT-COMPLETED QUESTIONNAIRES

Participants will complete a number of health related quality of life questionnaires at various time points throughout their participation in the trial (see Table 1). The following questionnaires will be included in each questionnaire pack, unless otherwise specified:

- **Gastrointestinal Quality of Life Index (GIQLI)**: Disease-specific HrQoL will be measured using the GIQLI. The GIQLI is composed of 36 items with 5 answer categories for each item (0-4). The GIQLI has been validated for use in patients with all gastrointestinal disease including colorectal disease requiring operative intervention [13, 14]. The GIQLI questionnaire will be included in the follow-up questionnaire packs only (i.e. at 30 days, 90 days, 6 months, 9 months and 12 months post-operation).

- **EQ-5D-5L™**: a well-validated questionnaire used to assess generic Quality of Life [15], it provides a simple descriptive profile and a single index value for health status.

- **SF-12®**: Generic HrQoL will be measured using the SF-12® questionnaire. SF-12® is a 12-item subset of the SF-36v2® that measures the same eight domains of health. The SF-12® is a well validated HrQoL tool for use in the acute setting with a short recall period of 1 week [16-18].

- **Health Resource Use**: is composed of questions related to contact with primary, community and social care services.

All participants will complete the health related quality of life questionnaire packs at baseline[5], 30 days, 90 days, 6 months, 9 months and 12 months post-operatively.

The baseline quality of life questionnaire pack will be completed by participants on paper at the participating local research site, either in A&E, surgical assessment units, surgical wards or in clinic. Participants will be asked to seal their completed baseline questionnaire pack in a pre-supplied envelope prior to giving it to the local research staff, who will then send the sealed envelope to the CTRU for entry into the trial database.

All subsequent questionnaire packs (30 days, 90 days, 6 months, 9 months and 12 months post-operation) will be administered directly to participants by the CTRU trial team. Participants will have the option to complete the post-operative questionnaires in paper format or electronically, depending on their personal preference. Participants who have chosen to complete their questionnaires in paper format will receive the questionnaire packs from the CTRU trial team by post and will be asked to return the completed questionnaires to the CTRU using a pre-supplied stamped, addressed envelope. For participants who choose to complete the questionnaires electronically, SMS and/or emails will be sent to the participants from the

[5] Baseline questionnaires must be completed after consent and, wherever possible, prior to randomisation (where this is not possible, they must be completed prior to the participant being made aware of their randomised treatment).

CTRU with the link to the questionnaire and to prompt completion. A thank you will be sent to participants by the CTRU upon receipt of a completed questionnaire. Should a completed questionnaire not be received at the CTRU by the required time-point, the CTRU will send one reminder to the participant either by post, SMS or email (depending on the participant's questionnaire-completion preferences).

11.6 DEATH

All deaths must be recorded on the Notification of Death eCRF. Data collected will include (but will not be limited to):

- Date of death
- Cause of death

Deaths occurring in the study population from the date of consent to 12 months post-operation must be reported on the **Notification of Death eCRF** on the LaCeS2 database **within 7 days** of site becoming aware of the event.

11.7 DEFINITION OF END OF TRIAL

The end of the trial is defined as the date of the last participant's last data item.

11.8 PROTOCOL DEVIATIONS

The CTRU undertake to adopt all reasonable measures to record data in accordance with the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control the CTRU. All such deviations will be documented on the study records, together with the reason for their occurrence; where appropriate, deviations will be detailed in the published report.

12 SAFETY REPORTING

For the purpose of this surgical trial, the safety reporting terms adverse events and serious adverse events have been translated into complications. The current evidence base suggests 30-day morbidity rates of 33-71% in patients undergoing an emergency laparotomy. Consequently, the proportion of patients experiencing complications and serious complications is anticipated to be high, reflecting current clinical practice.

All reported 30-day post-operative complications for the first 5 recruited patients at each site will be independently reviewed by the CTRU to ensure accurate reporting. Anticipated complications are outlined in Appendix 2, although this is not an exhaustive list.

12.1 GENERAL DEFINITIONS

A **complication** is defined as an untoward medical event in a participant, which has a causal relationship to the trial. The trial includes the surgical intervention and any trial specific interventions e.g. the consent process and completion of questionnaires.

An untoward medical event can include:

- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing condition
- any clinically relevant deterioration in any clinical tests

A **serious complication** is defined as a complication which:

- results in death
- is life-threatening[6]
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect, or
- is otherwise considered medically significant by the investigator

Serious complications occurring within 30 days of the participant's operation will be subject to expedited reporting requirements (see section 12.3 for further details).

An **Unexpected Serious Complication (USC)** is a **serious** complication which is **related** and **unexpected** and will require expedited reporting (see section 12.3) to enable reporting to the main Research Ethics Committee (REC) and Sponsor.

The Health Research Authority (HRA) defines the terms **related** and **unexpected** as:

- **Related**: that is, it resulted from administration of any research procedures. All complications by definition are related to the trial procedures. (Untoward medical events which are unrelated to the trial procedures are not being collected in this trial).

[6] Life-threatening refers to an event in which the participant was at risk of death at the time of the event, NOT an event which hypothetically may have caused death had it been more severe.

- **Unexpected**: that is, the type of event that in the opinion of the investigator is not considered expected. Examples of expected complications are provided in Appendix 2; note this is not an exhaustive list.

Medical and scientific judgement must be exercised in deciding whether an event is serious (see section 12.4 for Responsibilities). These characteristics/ consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

12.2 GRADING OF COMPLICATIONS

Intra-operative complications will be graded using the ClassIntra® classification of intraoperative adverse events [19]. Similar to the Clavien-Dindo classification for post-operative complications, ClassIntra® classifies intra-operative complications into 5 grades of increasing severity (see Appendix 4). Post-operative complications will be graded according to the Clavien-Dindo classification [20, 21]. This is an acceptable and validated method of documenting surgical complications. The system is divided into 7 grades (I, II, IIIa, IIIb, IVa, IVb and V), reflecting the varying severity of complications (see Appendix 3). The Clavien-Dindo classification grades the severity of complications by assigning a grade to the most severe complication. The Comprehensive Complication Index is a continuous measure which calculates the severity and grade of **all** experienced post-operative complications [22].

12.3 REPORTING OF COMPLICATIONS

Information on all complications which occur from the date of consent until the end of follow-up (12 months post-surgery) will be collected in this trial whether volunteered by the participant, discovered by investigator questioning or detected through physical examination or other investigation.

12.3.1 SERIOUS COMPLICATIONS (SCs) AND UNEXPECTED SERIOUS COMPLICATIONS (USCs) OCCURRING WITHIN 30 DAYS OF THE OPERATION – EXPEDITED REPORTING

All serious complications (SCs) and unexpected serious complications (USCs) (see section 12.1) which occur within 30 days of the operation are subject to expedited reporting requirements and must therefore be notified to the CTRU **within 24 hours** of the clinical research staff becoming aware of the event. Notifications must be sent to the CTRU by fax or email using the SC/USC CRF. Once all resulting queries have been resolved, the CTRU will request that the original form is posted to the CTRU and a copy retained at site.

24 hour fax for reporting SCs and USCs: 0113 343 6774

Email: ctru-laces@leeds.ac.uk

For each SC and USC, the following data will be collected:

- Start and end dates of event, if resolved
- Full details of complication in medical terms with a diagnosis
- Action/Intervention
- Outcome
- An identifiable and authorised reporting source (i.e. the signature of the investigator or other medic authorised by the investigator at the reporting research site)

Any follow-up information on SCs and USCs must be faxed or emailed to the CTRU as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached. All SCs and USCs will be reviewed by the Chief Investigator or delegate. USCs are subject to expedited reporting to the Sponsor and the main REC by the CTRU on behalf of the Chief Investigator in accordance with current NRES guidance, CTRU Standard Operating Procedures (SOPs), and Sponsor requirements.

SCs and USCs with an onset date greater than 30 days post-operation are not subject to expedited reporting, but must be reported with all other types of complication (i.e. non-serious expected and unexpected complications) on the standard post-operative follow-up eCRFs.

12.3.2 ALL OTHER COMPLICATIONS – NON-EXPEDITED REPORTING

Information about the incidence and severity of all other complications (this includes all non-serious expected and unexpected complications) which occur from the date of consent until 12 months post-operation will be collected for all participants on the Operative eCRF or on the Post-operative Follow-Up Assessment eCRFs, as appropriate. This also applies to any SCs or USCs with an onset date greater than 30 days post-operation. These events will **not** be subject to expedited reporting requirements.

12.3.3 UNTOWARD MEDICAL EVENTS UNRELATED TO THE STUDY

It is anticipated that there will be minimal additional risks associated with the interventions in this study. Participants treated may have co-morbidities and in recognition of this, untoward medical events will only be reported if they are classified as related to study procedures (including the surgical intervention and related procedures or study-specific procedures such as consent and questionnaire completion).

12.4 RESPONSIBILITIES FOR SAFETY REPORTING

Principal Investigator (PI) (i.e. lead study clinician at each recruiting research site or appropriate clinical individual identified in the Authorised Personnel Log)

- Checking for complications during admission and follow-up, including judgment in assigning:
    - Causality, i.e. whether an untoward medical event is related (i.e. a complication which therefore needs to be reported) or unrelated (i.e. not a complication and therefore does not need to be reported)
    - Seriousness
    - Expectedness
- To ensure that all SCs and USCs which occur within 30 days post-operation are recorded and initially reported to the CTRU within 24 hours of the research team becoming aware and to provide further follow-up information as soon as it is available.
- To report all other complications (SCs and USCs occurring beyond 30 days post-operation and non-serious complications) to the CTRU in line with the protocol during the trial follow-up period.
- To report USCs to local committees in line with local arrangements

Chief Investigator (CI) (or nominated individual in CI's absence)

- Assign relatedness and expected nature of reported complications/untoward medical events where it has not been possible to obtain local assessment.
- Undertake review of SCs and USCs (see section 12.3.1).
    - In the event of disagreement between local assessment and the CI, local assessment may be upgraded or downgraded by the CI prior to reporting to the REC.

Clinical Trials Research Unit (CTRU)

- Expedited reporting of USCs occurring within 30 days post-operation to the REC and Sponsor within required timelines.

- Preparing annual safety reports to the REC and periodic safety reports to the Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC) as appropriate
- Notifying Investigators of SCs and USCs which compromise participant safety.

Trial Steering Committee (TSC)

In accordance with the TSC Terms of Reference and CTRU policies, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

Data Monitoring and Ethics Committee (DMEC)

In accordance with the DMEC Terms of Reference and CTRU policies, periodic review of unblinded safety data to determine patterns and trends of events and to identify any safety issues which would not be apparent on an individual case basis.

13 OUTCOME MEASURES

13.1 PRIMARY OUTCOME MEASURE

The primary outcome measure of the LaCeS2 trial is the incidence of 30 day post-operative complications. This is defined as the number of patients with a post-operative complication (of any grade) occurring within 30 days of surgery as a proportion of all randomised patients.

13.2 KEY SECONDARY OUTCOME MEASURES

1) *Patient reported outcomes and Quality of Life Outcomes*

   All patient reported outcomes are collected during the 30 days, 3, 6, 9 & 12 months post-surgery.

a) ***12-Item Short Form Survey (SF-12)***

   This patient reported outcome consists of 12 items, covering 8 health domains (Physical Function, Role-physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-emotional & Mental Health), combined into physical & mental component scores (PCS & MCS).

b) ***Gastrointestinal Quality of Life Index (GIQLI)***

   The Gastrointestinal Quality of Life Index (GIQLI) questionnaire will be used to measure gastrointestinal related HRQoL [13] over the 12 month follow-up period. This questionnaire consists of 36 items, each scored between 0 – 4 points, to be summed up for a total aggregate score on the continuous scale 0 – 144, with 144 representing

best HRQoL [23]. In addition to the total score, there are also 5 subscales (GI symptoms, Emotion, Physical Function, Social Function & Medical Treatment), which can be summed to produce subscale scores [24].

13.3 SECONDARY OUTCOME MEASURES

2) 30-day post-operative complications severity

a) ***Clavien-Dindo (CD) Classification***

All post-operative complications will be graded according to the Clavien-Dindo (CD) Classification [20, 25]. This is an acceptable and validated method of documenting surgical complications. The CD Classification system assigns a grade to the most severe complication experienced. The system is divided into 7 grades (I, II, IIIa, IIIb, IVa, IVb and V), reflecting the varying severity of complications (Table 1, Appendix B).

b) ***Comprehensive Complication Index (CCI)***

The Comprehensive Complication Index [22] is used as a validated method to measure all complications experienced, measuring the overall magnitude of all complications experienced [26]. The CCI is calculated as the sum of all complications weighted by severity, measured using the CD classification for post-operative complications. The CCI is a continuous scale which ranks the severity of any combination of complications from 0 (no complications) to 100 (death) in a single patient.

3) 90-day post-operative and surgery specific complications

a) ***90-day post-operative complications***

The incidence of 90-day complications is defined as the number of patients with a complication occurring within 90 days post-operatively as a proportion of all randomised patients.

b) ***Surgery-specific complications***

The incidence of surgery-specific complications is calculated as the number of patients experiencing a surgery-specific complication within 6 & 12 months as a proportion of all randomised patients. Examples of surgery-specific complications are listed in Appendix 2, although the list is not exhaustive.

4) Intra-operative complications and intra-operative conversions from laparoscopic to open surgery

a) ***Intra-operative complications***

The incidence of intra-operative complications is defined as the number of patients with intra-operative complications recorded as a proportion of all randomised patients. Intra-operative complications will be graded according to the ClassIntra® v1.0 classification of intra-operative adverse events (see Appendix 4).

b) ***Intra-operative conversions from laparoscopic to open surgery***

An intra-operative conversion from laparoscopic to open surgery is defined as the use of a midline laparotomy wound for any part of the colorectal dissection during the procedure. The incidence of conversions from laparoscopic to open surgery is calculated as the number of patients experiencing a conversion as a proportion of all patients allocated to receive laparoscopic surgery.

5) Post-operative patient mortality, re-operations and readmissions

a) ***30-day post-operative mortality***

Mortality rates are defined as the number of patients that have been recorded as dead within the 30 days following surgery as a proportion of all randomised patients.

b) ***30-day post-operative re-operations***

The incidence of re-operations is defined as the number of patients that have recorded an additional abdominal surgical procedure within the 30 days following surgery as a proportion of all randomised patients.

c) ***30-day post-operative readmissions***

The incidence of 30 day post-operative readmissions is defined as the number of patients that have recorded a readmission to hospital following initial discharge within the 30 days following surgery as a proportion of all randomised patients.

6) Restoration of gastrointestinal function

a) ***Time to gastrointestinal function resumed***

Gastrointestinal function is defined as dietary intake (i.e. Consumption of food) AND bowel function (passage of stool) in keeping with the GI-2 definition [27]. Therefore, the time to restoration of gastrointestinal function is calculated as the time, in days, from surgery to dietary intake AND bowel function resumed.

7) Length of hospital stay

a) ***Time to discharge***

Length of hospital stay is calculated as the time, in days, from surgery to patient declared medically fit for discharge.

8) Cost-effectiveness

- EQ-5D-5L (30 days, 90 days, 6 months, 9 months and 12 months post-operation)
- Health resource utilisation assessed at 30 days, 90 days, 6 months, 9 months and 12 months post-operatively

9) Qualitative study

- An understanding of the recruitment barriers from the perspective of patients to inform staff/recruiter training.
- An understanding of the trial from the perspective of staff/recruiters at sites.

14 STATISTICAL CONSIDERATIONS

14.1 GENERAL CONSIDERATIONS

Statistical analysis is the responsibility of the CTRU Statistician (apart from the Health Economics analysis, details of which can be found in section 15). A full approved, version-controlled statistical analysis plan (SAP) will be written before any analyses are undertaken, according to guidelines published [28]. All analyses and patient populations will be predefined within the trial's SAP and reporting will be in line with CONSORT guidelines [29, 30]. As LaCeS2 is a superiority trial, the primary analysis will be based on an intention to treat (ITT) patient population, where all patients are analysed according to their randomised allocated treatment.

14.2 FREQUENCY OF ANALYSES

For the purposes of monitoring patient safety outcomes and data quality, interim reports will be completed on an annual basis for presentation to the DMEC. The DMEC will also monitor underlying assumptions of the statistical design, particularly the underlying assumptions of the control arm. Analyses will be agreed and documented upfront by the independent DMEC members. The DMEC, in the light of the interim data, and of any advice or evidence they wish to request, will advise the Trial Steering Committee if there is justification to consider closing the trial. No formal guidelines for stopping the trial early are in place since no formal interim analysis of the primary outcome measure is planned.

14.3 PRIMARY OUTCOME MEASURE ANALYSIS

The primary analysis of LaCeS2 will compare the primary outcome measure of the incidence of 30-day post-operative complications between patients randomised to undergo laparoscopic or open surgery. An adjusted treatment effect will be estimated using a multi-level logistic regression model, incorporating a random effect with respect to treating surgeon and adjusting for all minimisation factors listed above (Section 9.4). Statistical significance of the treatment effect within the statistical models will be based upon a 2-sided 5% level. This approach will be used to test a two-sided hypothesis that the complication rate is equal in both arms, suggesting an odds ratio equal to 1. Opposed to an alternative superiority hypothesis that the incidence of complications is 15% lower within those allocated to the laparoscopic surgery compared to those allocated to the open surgery group. A secondary analysis of the primary outcome measure will be performed where patients are analysed according to the actual surgery received (open, laparoscopic or laparoscopic converted to open surgery).

14.4 ANALYSES OF SECONDARY OUTCOME MEASURES

Secondary outcomes will be analysed according to the nature of the corresponding measures. Binary measures which include:

- Incidence of 90-day complications
- Surgery-specific complications within 6 & 12 months post-operatively
- Intra-operative complications

30-day post-operative mortality, re-operations and readmissions will be analysed differently from continuous measures which include:

- Patient-reported Quality of Life measures (SF-12 & GIQLI)
- Severity of 30-day post-operative complications, using CCI
- Time to restoration of gastrointestinal function
- Length of stay

Binary secondary outcome measures will be analysed using multi-level logistic regression models, adjusted for all minimisation factors whilst incorporating random effects with respect to treating surgeon. Adjusted treatment effects will be reported alongside 95% confidence limits.

Continuous secondary outcome measures will be analysed using multi-level linear models, adjusted for all minimisation factors whilst incorporating random effects with respect to treating surgeon. Models for the patient reported outcomes (SF-12 & GIQLI) will include an additional level to account for repeated measures due to the longitudinal nature of the data.

14.5 MISSING DATA

The underlying mechanism of missing data and reasons for missing-ness will be scrutinised to assess the assumption of missing at random. Missing outcome data may be imputed dependent on level of missing-ness. Details on the model and method used for missing data will be specified within the SAP, finalised before analysis.

14.6 SAMPLE SIZE

The trial design, sample size and power calculations are informed by the previous LaCeS feasibility trial [10, 31], based upon a superiority hypothesis for the primary outcome measure. Secondary outcome measures are not powered. The incidence of 30-day complication rates was estimated in LaCeS feasibility as 41.9% (95% CI 24.6%, 60.9%) in the open surgery group (31 pts). Based on clinical consensus of the applicants, an absolute reduction of at least 15% is considered achievable and represents the minimum clinically relevant difference required to change practice.

512 patients are required in total to detect a 15% absolute reduction in the incidence of 30-day complications with 90% power and a 5% 2-sided significance level, using a two-group continuity corrected chi-squared test of equal proportions. This assumes an incidence of 30-day complications of 45% in the open surgery arm, based on results of LaCeS feasibility, literature [2, 3] and clinical opinion, and accounts for a 10% drop-out, as observed in LaCeS feasibility (nQuery Advisor v7.0). At least 88% power will be achieved to detect a 15% absolute reduction should the incidence of complications in the open surgery arm be higher than observed in LaCeS feasibility (up to 60%). The external, independent Data Monitoring Committee will monitor the underlying sample size assumptions at the end of the pilot phase.

15 HEALTH ECONOMIC EVALUATION

The economic evaluation will compare laparoscopic with open colorectal surgery adhering to the NICE reference case [32]. The primary end-point will be cost per incremental quality-adjusted life year (QALY) and the perspective that of the health and personal social service (PSS) provider. A supplementary analysis will adopt a wider perspective and incorporate patient and carer costs. We will report incremental cost-effectiveness ratios (ICERs) [33] at trial end (12 months) however the primary end-point will be based on lifetime expected costs and outcomes generated from a de novo decision analytic model. Our analysis will be detailed in a Health Economic Analysis Plan (HEAP) and will mirror the approach of the statistical analysis plan and analyse the intention to treat sample (based on randomisation) but also conduct supplementary analysis evaluating actual surgery received (open, laparoscopic or laparoscopic converted to open surgery).

Costs and outcomes

Resource use and utility data will be captured in the trial at baseline and each follow-up assessment point.

We will conduct a micro-costing of the interventions based on CRF data on theatre time and staff involvement (staff number, type and grade). Data on hospital visits (inpatient and outpatient) and length of stay up to 12 months will be collected using CRFs which will also capture detail on ward type and whether critical care was required. Primary (e.g. GP contact and district nurse visits) and social care (e.g. social worker and home help) resource use will be captured on a patient completed form. This strategy proved successful in the feasibility study and limited missing data. This form will also capture data on patient and carer costs incurred in the receipt of health care. Unit costs will be taken from the PSSRU report, NHS Reference costs and participating trust finance departments.

Utility will be captured using the EQ-5D-5L [15]. Currently, NICE advise the use of a published (EQ-5D-5L to EQ-5D-3L) mapping algorithm to generate the utility index from the EQ-5D-5L [34] [35]. However, a new valuation study is on-going [36]and we will use the new UK valuation tariff when this is available, providing the results are valid and robust. A supplementary analysis will explore basing quality-adjustment based on the SF-6D (derived from the SF-12) [37]. We will use an area under the curve approach to estimating 12 months QALYs.

Trial analysis

We will use seemingly unrelated regression models to analyse cost and QALY data during the trial follow-up, allowing us to account for the correlation between the two outcomes. Where appropriate, we will mirror the statistical approach to incorporating control variables and adjust for the specified minimisation factors. We will also adjust for any imbalance in baseline costs and utility if necessary. The analysis will account for clustering at surgeon level and employ a multi-level model [38]. Parametric or non-parametric (i.e. bootstrapping) methods will be used to characterise the sampling uncertainty present with simulations plotted on a cost-effectiveness plane and cost-effectiveness acceptability curves.

We will assess the type and degree of missing data and evaluate whether the assumption of missing at random (MAR) holds [39]. If that is the case, multiple imputation will be used to impute missing data. Should MAR not hold we will explore the impact of alternative assumptions [40].

Decision model

As the benefits of the interventions are expected to extend beyond the trial follow-up period, we will develop a decision-analytic model to estimate future costs and benefits following best practice [41]. The model type and structure will be agreed after consultation with clinical experts and patients and a review of existing models in the area. The model development process will determine whether one decision model will be sufficient or if other sub-models are required to capture relevant long-term impacts of the different colorectal pathologies (e.g. disease free vs. recurrence health states in cancer [42] and specific long term complications in inflammatory bowel disease). We will develop a model outline document distinct from the HEAP and in collaboration with the team to detail the model structure, parameters and analytical approach.

Twelve month cumulative cost and QALY data (and related variance) generated from the trial will feed into the model at initiation. We will use trial data and targeted literature reviews to derive health state parameters and use NELA to derive additional parameters of interest (e.g. relating to learning effects). The model will enable the calculation of discounted lifetime ICERs and estimates of net monetary benefit (NMB). We will assume a cost-effectiveness threshold of £20,000 per QALY gained. We will conduct extensive deterministic one-way and scenario sensitivity analyses which will allow us to explore, for example, the impact of surgeon learning curves and alternative implementation scenarios on cost-effectiveness. Monte Carlo simulations using draws from parameter distributions will allow a probabilistic sensitivity analysis capturing total parameter uncertainty in the model. Results from this will be presented in the form of cost-effectiveness planes, NMB distributions and cost-effectiveness acceptability frontiers [43].

Costs and benefits post 12 months will be discounted at a rate of 3.5% per annum as per NICE guidance. All reporting of results will conform to published guidelines [44] [45].

16 TRIAL MONITORING

Trial supervision will be established according to the principles of GCP and in-line with the NHS UK Policy Framework for Health and Social Care. This will include establishment of a core Project Team, Trial Management Group (TMG), an independent TSC and independent DMEC. A Trial Monitoring Plan will be developed based on the trial risk assessment; this may include site monitoring.

16.1 TRIAL STEERING COMMITTEE (TSC) & DATA MONITORING AND ETHICS COMMITTEE (DMEC)

An independent DMEC will be appointed to review the safety and ethics of the trial, alongside trial progress and overall direction as overseen by the TSC. Detailed un-blinded reports will be prepared by the CTRU for the DMEC at approximately yearly intervals.

The DMEC will report to the TSC, who will remain blind and will have overall external oversight of the trial (ensuring regular reports to the NIHR Health Technology Assessment (HTA) Programme). Further details about the responsibilities of each committee can be found in section 20.1.

16.2 DATA MONITORING

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until they are received, until confirmed as not available, or until the trial is at analysis.
The CTRU or Sponsor will reserve the right to intermittently conduct source data verification (SDV) exercises on a sample of participants, which will be carried out by staff from the CTRU or Sponsor. SDV will involve direct access to participant medical notes at the participating research sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

A Trial Monitoring Plan will be developed.

16.3 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by participants during the trial period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual research sites.

17 QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

17.1 QUALITY ASSURANCE

The trial will be conducted in accordance with the principles of GCP in clinical trials, the NHS UK Policy Framework for Health and Social Care and through adherence to CTRU SOPs.

17.2 SERIOUS BREACHES

The CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to **immediately** notify the CTRU of a serious breach (as defined in the latest version of the HRA SOP) that they become aware of. A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree-

a) the safety or physical or mental integrity of the trial subjects, or

b) the scientific value of the research

In the event of doubt or for further information, the Investigator should contact the Senior Trial Manager at the CTRU.

17.3 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013. Informed written consent will be obtained from the participants prior to randomisation into the trial. The right of a patient to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment.

Ethical approval will be sought through the Health Research Authority (HRA). The trial will be submitted to and approved by a REC, the HRA and the appropriate Site Specific Assessor for each participating research site prior to entering participants into the trial. The CTRU will provide the REC with a copy of the final protocol, participant information sheets, consent forms and all other relevant trial documentation.

18 INFORMATION GOVERNANCE AND CONFIDENTIALITY

The University of Leeds is the data controller for the trial. The University of Leeds and the University of Hull will be joint data controllers for the data relating to the qualitative sub-study. Participating sites will be data processors for any trial data processing (while remaining data controllers of data processing required for patient care).

All data processing for the trial will be in accordance with the 2018 Data Protection Act. Personal data will be processed under a lawful basis of 'task in the public interest' (GDPR Article 6, 1(e)) and special categories of personal data (in this case, data about health, racial or ethnic origin and genetic data) will be processed for scientific research purposes (GDPR Article 9, 2(j)).

All trial participants (and any patients considered for the trial) are provided with detailed information about how their data will be processed before any trial data processing. Any material changes to how data will be processed will be communicated to trial participants in a timely manner (prior to the changes, if reasonably possible).

Personal data will only be processed for specified, explicit and legitimate purposes, and will be adequate, relevant and limited to those purposes. Data will be stored and transferred securely for all processing. The trial will undergo an information governance risk assessment at the CTRU to ensure its proposed processing is compliant with data protection laws.

Confidentiality of participant data will be maintained at all times, with access to data granted only to those who need it for legitimate reasons (i.e. to conduct the trial, or to ensure the trial has been conducted lawfully). Participants will allow access to their confidential data through the informed consent process. Copies of participants' consent forms, which will include participants' full names, will be collected when a participant is randomised into the trial by the CTRU. In addition, participant name and address may be collected for questionnaire-posting or email address/telephone number if the participant chooses to complete the questionnaires electronically. All other data collection forms that are transferred to or from the CTRU will be coded with a unique participant trial number and will include two participant identifiers, usually the participant's initials and date of birth. Data will be held securely on paper and electronically at the Clinical Trials Research Unit (CTRU). The CTRU will have access to the entire database for monitoring, co-ordinating, and analysis purposes.

Sites are responsible for maintaining this pseudonymisation on any data sent to the CTRU. Any exceptions (e.g. collecting unredacted consent forms at the CTRU for central monitoring of informed consent) will only be for legitimate reasons and will be explained fully to participants in advance of data processing. Where central monitoring of source documents, or copies of source documents, is required by CTRU, the participant's name must be obliterated by site before sending. Any breach of confidentiality or of participants' personal data will be handled and reported (if required) in line with relevant laws.

Data will be made available for secondary research once the main trial objectives are complete.

If a participant withdraws consent from further trial treatment and/or further collection of data, their data will remain on file and will be included in the final trial analysis.

Participant health data will also be obtained from the National Emergency Laparotomy Audit (NELA), a standard patient registry that is used by the NHS and held by NHS England and the Healthcare Quality Improvement Partnership (HQIP). This data will be collected for the purposes of the SWAT relating to the integration of routine data (see section 23.1) and will not be used for any other purpose. NELA have strict rules about sharing their data. You can find out more at https://www.nela.org.uk/NELA_Privacy_Policy. The data collected from NELA will be stored securely at the CTRU and will only be accessed by authorised members of the trial team. The data will be pseudonymised and will be linked using three participant identifiers (date of birth, NHS number and NELA ID).

18.1 ARCHIVING

18.1.1 TRIAL DATA AND DOCUMENTS HELD BY CTRU

At the end of the trial, all data held by the CTRU and all trial data will then be securely archived at the University of Leeds in line with the Sponsor's procedures for a minimum of 5 years. When there is no longer a lawful basis for retaining the data, it will be securely destroyed.

18.1.2. TRIAL DATA AND DOCUMENTS HELD BY RESEARCH SITES

Research sites are responsible for archiving all trial data and documents (ISF and all essential documents therein, including CRFs) at the participating research site until authorisation is issued from the Sponsor for confidential destruction.

18.1.3 PARTICIPANT MEDICAL RECORDS HELD BY RESEARCH SITES

Research sites are responsible for archiving trial participant medical records in accordance with the site's policy and procedures for archiving medical records of patients who have participated in a clinical trial. However, participant medical records must be retained until authorisation is received from the Sponsor for confidential destruction of trial documentation.

19 STATEMENT OF INDEMNITY

The University of Leeds is able to provide insurance to cover for liabilities and prospective liabilities arising from negligent harm. Clinical negligence indemnification for UK sites will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

20 TRIAL ORGANISATIONAL STRUCTURE

Research sites will liaise with the CTRU for advice and support on trial set-up and operation, and submission of trial data. In turn, the CTRU will be responsible for data chasing.

20.1 OPERATIONAL STRUCTURE

Chief Investigator (CI): As defined by the NHS UK Policy Framework for Health and Social Care, the CI is responsible for the design, management and reporting of the trial.

Trial Sponsor - University of Leeds: The Sponsor is responsible for trial initiation management and financing of the trial as defined by the Directive 2001/20/EC. The sponsor delegates some of these responsibilities to CTRU as detailed in the trial contract.

Clinical Trials Research Unit (CTRU): the CTRU at the University of Leeds will have responsibility for the conduct of the trial in accordance with the NHS UK Policy Framework for Health and Social Care and CTRU SOPs. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs and the NHS UK Policy Framework for Health and Social Care including randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, ongoing management including training, monitoring reports and trial promotion, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support ethical approval submissions, any other site-specific approvals, and clinical set-up. The CTRU will be responsible for the overall day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting, and all statistical analyses. At the end of the trial, CTRU will be responsible for archiving all data and trial data held by the CTRU in line with the Sponsor's procedures for a minimum of 5 years.

Research Sites (local PI): The responsibility for ensuring clinical management of participants is conducted in accordance with the trial protocol ultimately remains with the PI at each research site.

20.2 OVERSIGHT/TRIAL MONITORING GROUPS

Trial Management Group (TMG): the TMG, comprising the CI, CTRU team, other key external members of staff involved in the trial, and a patient representative will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation of results. Specifically the TMG will be responsible for:

- Protocol completion
- CRF development
- Obtaining approval from the HRA, UK REC and supporting applications for Site Specific Assessments (SSAs)
- Completing cost estimates and project initiation
- Nominating members and facilitating the TSC and DMEC
- Reporting of complications
- Monitoring of screening, recruitment, treatment and follow-up procedures
- Auditing consent procedures, data collection, trial end-point validation and database development.

Trial Steering Committee (TSC): the TSC will have overall responsibility for the external oversight of the trial. The TSC will provide overall blinded monitoring of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an independent Chair, not less than two other independent members, and a consumer representative. The CI and other members of the TMG may attend the TSC meetings and present and report progress. The independent Committee will meet annually as a minimum and will consider recommendations made by the independent DMEC.

Data Monitoring and Ethics Committee (DMEC): the independent DMEC will review the safety of participants and ethics of the trial by reviewing interim data during recruitment and follow-up. The DMEC will be comprised of between 3 and 5 independent voting members, at least one of whom will be a statistician, and at least one of whom will be a clinician experienced in the relevant area; one DMEC member will assume the role of Chair. DMEC meetings will consist of an open session to discuss aggregate data with the wider trial team and, a closed session, where data (as agreed and specified in the DMEC Charter) will be presented by randomised group and discussed only with the Trial Statisticians. The Committee will meet annually as a minimum and make recommendation regarding continuation, specifically following the internal pilot phase to the TSC.

Public Patient Involvement (PPI): A PPI representative will sit on the Trial Management Group and there will also be a PPI representative on the Trial Steering Committee. The PPI

representatives will advise on aspects of the trial affecting patient participation and review patient documentation.

20.3 FUNDING

This project is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme (Grant Ref: NIHR128815).The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

21 PUBLICATION POLICY

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Authorship decisions will be guided by standard requirements for authorship relating to submission of manuscripts to medical journals. These state that authorship credit should be based only on the following conditions being met (http://www.icmje.org):

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Substantial contribution to drafting the article or revising it critically for important intellectual content
- Substantial contribution to final approval of the version to be published.

In light of this, the CI, other grant co-applicants, and relevant senior CTRU staff will be named as authors in any publication, subject to journal authorship restrictions. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial. It is planned that the top five recruiting LaCeS2 research site staff will be named as authors. In addition, LaCeS2 publications will be published on behalf of the LaCeS2 Group. All PIs and associate PIs from participating sites who achieve their minimum recruitment target (12 participants per year) will be included as members of the LaCeS2 Group.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral

presentation purposes, without the permission of the TSC. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

On completion of the research project a draft final report will be submitted to the HTA programme (trial funder) by the CTRU, within 14 days. This will be peer reviewed and then published on the HTA website. The CTRU is obliged to provide NIHR/HTA with advanced notice of any publication relating to the trial. Copies of any materials intended for publication will be provided to NIHR/HTA at least 28 days prior to submission for publication.

22 QUALITATIVE SUB-STUDY

22.1 PATIENT AND STAFF VIEWS OF THE LACES2 STUDY

22.1.1 BACKGROUND

Our feasibility study was conducted in sites with a strong track record of laparoscopic surgery [10] and we found clinicians could struggle with presenting the trial to some patient groups [31]. Widening recruitment to other sites is likely to identify new recruitment challenges, so LaCeS2 includes integrated qualitative work to prospectively identify and address these challenges in the new sites. It is well recognised that training health professionals to recruit to trials helps recruitment. We also know that each site will have its own challenges and so we will prospectively identify challenges and use the learning from this work, and our previous work to develop a tailored staff recruitment training package to deliver in sites, informed by the Quintet programme [46], [47], [48], [49].

The Quintet programme identified a range of recruitment challenges, such as patient preferences, how to discuss trial terminology (e.g. what is randomisation? Why randomise?), how to provide complex information about trials to different patient groups, gaining authentic informed consent [50]. Our own research also identified other key barriers, including a lack of patient equipoise, a reluctance to approach unwell or complex patients (and reluctance to use patient advocate consent), and more practical issues such as a lack of on-call surgeon, research nurse time, and a lack of experience recruiting to trials, and in smaller centres, access to operating theatres [11]. We anticipate that other challenges will be identified when we talk with new centres, some of which will be new to surgical trials.

In the feasibility study we interviewed patients who consented to participate in the study and identified ways to improve the experience for participants and adapted our study design to

accommodate these changes [31]. Our feasibility work identified reasons patients consented to trial participation, but in the feasibility study there were few trial decliners and none consented to interview, so we have limited understanding of their reasons for declining. Studies show we can learn a lot from trial decliners about how a trial invitation is presented and received, and this knowledge can be used to improve recruitment [51]. Therefore, in this sub-study we will seek to recruit people who decline trial participation to understand their reasons, and if possible adapt our recruitment processes to improve patient experience. As we have made changes to the study design following the feasibility study, we will also seek to interview consenters to ensure that the changes we have made and the recruitment materials we will use in this study are acceptable to patients.

22.1.2 AIM

To understand the trial from the perspective of patients and recruiters and adapt recruitment processes to improve recruitment. These findings will be used to develop a bespoke training package for recruitment staff.

22.1.3 DESIGN

Cross-sectional in-depth semi-structured interviews.

22.1.4 ELIGIBILITY AND SAMPLING

22.1.4.1 SITE ELIGIBILITY

All sites recruiting to the LaCeS2 trial will take part in this sub-study.

22.1.4.2 PATIENT ELIGIBILITY

Patients from all sites who consent or decline trial participation during the pilot phase will be eligible to participate.

22.1.4.3 STAFF ELIGIBILITY

Staff involved in LaCeS2 recruitment will be eligible to participate.

22.1.4.4 SAMPLING

A purposive sample of patients approached for the trial will be recruited (10-12 decliners, and up to 30 consenters), where possible representing males and females with a range of ages and clinical presentations.

A random sample of 20-25 staff involved in recruiting to the trial from a range of centres will be recruited. Staff to be sampled include: local principal investigators, research nurses, surgical trainees and other surgeons who will recruit to the study.

22.1.5 RECRUITMENT AND DATA COLLECTION PROCESSES (PATIENTS)

During the internal pilot phase, all patients approached for the trial (decliners and consenters) will be invited to take part in an interview to gather their views on the trial recruitment processes and intervention. Patients may consent immediately, decline immediately, or defer their consent.

If a patient consents immediately, a member of the local research team will forward information to the qualitative research team and arrangements will be made to interview the patient, either while the patient is in hospital, or post-discharge, as appropriate. If a patient defers consent, verbal consent for the qualitative researcher to receive their contact details and to re-approach the patient post-discharge will be sought by the local research team and noted on the recruitment log. Sites will pass patient contact information and copies of participant consent forms (where applicable) to the qualitative research team using a secure drop box facility. In the event that a patient is not approached at all about the sub-study prior to discharge, the local site research team will send out an invitation letter introducing the sub-study to the patient alongside the relevant Participant Information Sheet and an expression of interest form. If the patient is interested in taking part in an interview and is happy to be contacted by a member of the qualitative research team to discuss further, the patient can complete the expression of interest form with their contact details and return this to the qualitative research team either directly by post or via the LaCeS2 research team at their hospital. Alternatively, a member of the local site research team may contact the patient by telephone to confirm that the patient is happy for their contact details to be passed onto the qualitative research team.

The qualitative researcher will contact all patients who consent or agree to contact by phone or post, as appropriate. Any patients who verbally give consent to contact and agree to take part in the sub-study, will be asked to sign a consent form wherever possible; if it is not possible for the patient to sign the consent form prior to the date of the interview e.g. because of COVID-19 restrictions, verbal consent will be taken at the start of the interview instead, and the section of audio file that goes through the consent process will be saved.

Trial decliners and consenters who consent to interview will be invited to participate in a face-to-face, telephone or video chat interview (depending on patient preference and COVID-19 restrictions). Interviews will be guided by a topic guide developed for the study to explore their response to the trial invitation, and the information materials provided to them, in order to

understand their decision, and improve trial processes. Interviews are likely to take place post-discharge, but researchers will be flexible to patient wishes (e.g. if patients wish to be interviewed whilst still in hospital this will be accommodated, if feasible).

22.1.6 RECRUITMENT AND DATA COLLECTION PROCESSES (STAFF)

Staff will be recruited via the local principal investigator, with support from local R&D offices. All sites will be aware of their involvement in the trial prior to contact being made with the local principal investigator. A participant information sheet explains the qualitative study and invites the team to identify team members for interview. Interview respondents will be selected from those who respond to the interview invitation and will be selected to ensure the following characteristics are represented: new/experienced recruiters; junior/senior staff; nurses and doctors.

Telephone/online interviews will take place during the internal pilot phase. Interviews will use a topic guide informed by the findings of our feasibility study [11] and the Quintet intervention [50] to assess their knowledge of the evidence base for laparoscopic surgery, their understanding of equipoise, and generate a discussion of the recruitment materials and how the pathway and protocol fit with their clinical practice. The interviewer will identify local level recruitment barriers and work with sites to put in place potential solutions that can be implemented locally.

22.1.7 DATA ANALYSIS

Interviews will be audio-recorded, with participant permission, and transcribed verbatim. Transcripts will be anonymised at point of transcription. NVivo qualitative data analysis software will be used to store and manage the transcripts during analysis. Deductive thematic data analysis will be undertaken with transcripts coded by ascribing words and phrases to capture the meaning in the text to identify common emerging ideas [52]. To ensure reliability in the coding a subset of transcripts will be dual coded by two researchers and any discrepancies discussed until consensus reached. A coding index will be developed using the first five transcripts and applied to the remaining transcripts. The analysis will focus on identifying recruiter and patient attitudes or behaviours that are amenable to change, and views of the recruitment materials. One researcher will lead on the analysis, with regular meetings with the qualitative lead and Chief investigator overseeing the process. The analysis will be undertaken in parallel with data collection so data analysis can inform later sampling decisions and interview questions.

22.1.8 OUTPUTS

Emerging findings will be fed back to the TMG and all sites in an ongoing manner, to aid recruitment during the pilot study, and additional training for staff implemented, if needed. Findings will be reported to the DMEC at the end of the pilot phase to inform DMEC recommendations at that time.

Findings from the staff interviews will be used along with data from our feasibility study to help develop a training programme which will be delivered to local research site staff at each site, throughout the trial to refresh their training, and offer training to new staff joining the trial (see section 23.3 for further details).

Staff training will be offered as face-to-face or telephone support. If, in the light of COVID, face-to-face training is not possible, an online training resource will be developed using a combination of pre-recorded presentations and online discussions.

23 STUDY WITHIN A TRIAL (SWAT)

Emergency surgery trials have been regarded to be difficult to run due to a number of perceived difficulties including acceptable recruitment, timely randomisation, attrition, safety and clinician and patient equipoise. The timely delivery of definitive clinical care to an unwell cohort of patients must be prioritised over trial-related processes. To address some of the practical and logistical issues associated with running surgical trials in the emergency setting a SWAT will be carried out to examine strategies to maximise efficiency in emergency surgery trials.

23.1 INTEGRATION OF ROUTINE DATA

An assessment of the feasibility, quality and accuracy of collecting trial-related data from routine data from the National Emergency Laparotomy Audit (NELA) will be undertaken. Case report forms (CRFs) are currently considered the gold standard for collecting trial-specific data and the LaCeS Feasibility Trial reported a data compliance rate of over 95% for the operative CRF. The aim of this study is to externally validate the use of NELA as a data collection platform for surgical trials by comparing its data ascertainment and accuracy with the standard trial CRFs for all LaCeS2 participants recruited at sites in England and Wales.

23.2 OPTIMISING RECRUITMENT STRATEGIES IN THE EMERGENCY SETTING

During the LaCeS2 recruitment period, we will try to identify the most effective method(s) of recruitment. Recruitment strategies may include videos, patient stories & clinician-led recruitment, with sites receiving one or more of these interventions. The impact of these strategies will be analysed quantitatively by evaluating recruitment rates, and the implementation and acceptability of these strategies may also be evaluated qualitatively through other aspects of the embedded qualitative work. Where relevant, the findings of this study will feed into the development of the evolving site training package, which will be used to provide additional recruitment support to sites on an ongoing basis throughout the trial (see section 23.3).

23.3 SITE TRAINING PACKAGE

An emergency-trial-specific training package for local research teams to help them identify, approach and recruit patients will be developed and delivered to sites at site opening and on an ongoing basis throughout the recruitment period. The initial training package will be informed by the findings of the LaCeS Feasibility Trial but this training will be updated as the trial progresses based on emerging findings from other aspects of the embedded qualitative work e.g. interviews with trial consenters and decliners (section 22), site staff interviews (section 22) and the evaluation of effective recruitment strategies (section 23.2).

24 ABBREVIATIONS USED

ACRONYM	DEFINITION
AHRQ	Agency for Healthcare Research and Quality
ACPGBI	Association of Coloproctology of Great Britain and Ireland
APL	Authorised Personnel Log
ARDS	Acute Respiratory Distress Syndrome
ASA	American Society of Anaesthesiologists
AXR	Abdominal X-Ray
CCI	Comprehensive Complication Index
CI	Chief Investigator
CNS	Central Nervous System
CONSORT	Consolidated Standards Of Reporting Trials
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CT	Computed Tomography
CTPA	Computed Tomography Pulmonary Angiogram
CTRU	Clinical Trials Research Unit
CVA	Cerebrovascular Accident
CXR	Chest X-Ray
DMEC	Data Monitoring and Ethics Committee
DVT	Deep Vein Thrombosis
ECG	Echocardiogram
GCP	Good Clinical Practice
CD	Clavien-Dindo
GDPR	General Data Protection Regulation
GI	Gastrointestinal
GIQLI	Gastrointestinal Quality of Life Index
GP	General Practitioner
HEAP	Health Economic Analysis Plan
HQIP	Healthcare Quality Improvement Partnership
HR	Heart Rate
HRA	Health Research Authority
HTA	Health Technology Assessment

HrQoL	Health Related Quality of Life
ICER	Incremental Cost-effectiveness Ratio
ICMJE	International Committee of Medical Journal Editors
IC	Intermediate Care
ICU	Intensive Care Unit
ID	Identification
ISF	Investigator Site File
ITT	Intention to Treat
LGI	Lower Gastrointestinal
MAR	Missing at Random
MCS	Mental Component Score
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NB	Nota Bene
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NELA	National Emergency Laparotomy Audit
NHS	National Health Service
NICE	National Institute for Healthcare and Excellence
NIHR	National Institute for Health and Care Research
NMB	Net Monetary Benefit
NRES	National Research Ethics Service
PCS	Physical Component Score
PI	Principal Investigator
PIN	Personal Identification Number
PIS	Patient Information Sheet
PPI	Patient Public Involvement
PSI	Patient Safety Indicators
PSS	Personal Social Service
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RR	Respiratory Rate
NRES	National Research Ethics Committee
RDE	Remote Data Entry

SAP	Statistical Analysis Plan
SC	Serious Complication
SDV	Source Data Verification
SMS	Short Message Service
SOP	Standard Operating Procedure
SSI	Surgical Site Infection
SSOP	Standard Site Operating Procedure
SWAT	Study Within A Trial
TMG	Trial Management Group
TSC	Trial Steering Committee
UGI	Upper Gastrointestinal
UK	United Kingdom
USC	Unexpected Serious Complication
USS	Ultrasound Scan
WCC	White Cell Count

25 APPENDICES

Appendix 1 Classifications of Intervention

The NCEPOD Classification of Intervention

IMMEDIATE – Immediate life, limb or organ-saving intervention – resuscitation simultaneous with intervention. Normally within minutes of decision to operate. A) Life-saving B) Other e.g. limb or organ saving

URGENT – Intervention for acute onset or clinical deterioration of potentially life-threatening conditions, for those conditions that may threaten the survival of limb or organ, for fixation of many fractures and for relief of pain or other distressing symptoms. Normally within hours of decision to operate.

EXPEDITED – Patient requiring early treatment where the condition is not an immediate threat to life, limb or organ survival. Normally within days of decision to operate.

ELECTIVE – Intervention planned or booked in advance of routine admission to hospital. Timing to suit patient, hospital and staff.

NELA urgency of surgical intervention sub-categories

- 3. Expedited (>18 hours)
- 2B. Urgent (6-18 hours)
- 2A. Urgent (2-6 hours)
- 1. Immediate (<2 hours)

Appendix 2 – Definitions of Expected Complications

NB: This is not an exhaustive list

INTRA-OPERATIVE

- **Visceral Injury**

  Visceral injury is defined as any iatrogenic injury to the intestines, bladder, ureters or neurovascular structures.

- **Haemorrhage**

  Intra-operative haemorrhage is defined as more than 0.5 litres of expected blood loss during the operation.

- **Carbon Dioxide Embolism**

POST-OPERATIVE

- **Ileus**
  - Clinical Features: abdominal distension, constipation, vomiting or high nasogastric tube output.
  - Radiological (AXR or CT scan) features in keeping with post-operative ileus.
  - Physician diagnosis of ileus.
- **Anastomotic Leak**
  - Clinical evidence of anastomotic leak e.g. faeces draining per drain.
  - Radiological diagnosis of anastomotic leak.
  - Surgical evidence of faecal contamination and anastomotic disruption at relaparotomy.
- **Gastrointestinal Obstruction**
  - Clinical features of abdominal pain, abdominal distension, vomiting or high nasogastric tube output or constipation.
  - Radiological evidence of obstruction.
  - Surgical evidence of obstruction at re-operation
- **Gastrointestinal Haemorrhage**
  - Postoperative bleeding (overt blood loss requiring > 2litre transfusion with normal clotting profile)
  - Clinical features of malaena/haematemesis/per rectal bleeding.
  - Re-operation with confirmed source of GI bleeding.
  - Endoscopic (UGI/LGI endoscopy) confirmation of GI bleeding source.
  - CT angiography confirming GI bleeding.
- **Gastrointestinal ischaemia/necrosis**
  - Necrosis of stoma requiring re-operation

- **Gastrointestinal perforation**
    - Radiological (CXR or CT scan) evidence of perforation.
    - Evidence of GI perforation at re-operation.
- **Wound Infection**

  Superficial Surgical Site Infection

  Superficial Surgical Site Infection (SSI) is an infection that occurs within 30 days postoperatively and infection involves only skin or subcutaneous tissue of the incision and at least one of the following:
    - Purulent discharge.
    - Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
    - At least one of the following signs or symptoms of infection:
        - Pain/Tenderness
        - Localised swelling
        - Erythema
        - Superficial incision is deliberately opened by the surgeon
        - Diagnosis of superficial SSI by Surgeon

  Deep Incisional SSI

  Deep Incisional SSI is an infection that occurs within 30 days after the operation and the infection appears to be related to the operation and infection involved deep soft tissues (muscle/fascial layers) and at least one of the following:
    - Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
    - A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms:
        - Fever >38
        - Localised pain/tenderness
        - An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiological examination.
        - Diagnosis of a deep SSI by a surgeon.

  Organ/Space SSI

  Organ/Space SSI is an infection that occurs within 30 days after the operation and the infection appears to be related to the operation and the infection involves any part of the anatomy (organs or space), other than the incision, which was opened and manipulated during an operation and at least one of the following:
    - Purulent discharge from a drain that is placed through a stab wound into the organ/space.

- Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
- An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathology or radiological examination.
- Diagnosis of an organ/space SSI by a surgeon.

- **Wound Dehiscence**
  - Separation of the layers of a surgical wound, which may be partial or complete, with disruption of the fascia.

RESPIRATORY

- **Respiratory Failure/Acute Respiratory Distress**

  Patients with respiratory failure/acute respiratory distress must meet the following criteria:
  - Acute onset
  - CXR: Bilateral infiltrates
  - Lack of clinical congestive heart failure
  - Refractory hypoxaemia Pa02:Fi02< 200 for ARDS.
  - Evidence of respiratory failure on arterial blood gas (e.g. PaO2 <8KPa +/- PaCO2 >6KPa)
  - Mechanical ventilation for >24hrs.

- **Pneumonia**

  Patients with pneumonia must meet criteria from both Radiology and Clinical Features/Laboratory reports.
  - Radiology:

    One definitive chest radiography (CXR) or CT scan with at least one of the following:
    - New or progressive and persistent infiltrate
    - Consolidation or opacity
    - Cavitation
  - Clinical Features/Laboratory Reports

    At least one of the following:
    - Temperature <36 or >38
    - WCC < 4 or >12
    - For adults over 70 years old, acute confusional state

    And, at least two of the following:
    - New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions or increased suctioning requirements

- New onset of worsening cough or shortness of breath
- Localising signs on auscultation of the chest (e.g. bronchial breathing, crepitations)
- Worsening gas exchange (e.g. O2 desaturations), increasing oxygen requirements, or increased ventilator demand.

- **Pulmonary Embolus/DVT**

  Patients must fulfil the following criteria
  - Clinical Features: Acute breathlessness, pleuritic chest pain, haemoptysis, calf pain or swelling.
  - ECG: Sinus tachycardia, new onset right bundle branch block, right ventricular strain (T wave inversion V1-3).
  - Radiology: Radiological confirmation on CTPA or V/Q scan of pulmonary embolus. Duplex USS scan confirmation of DVT.

- **Atelectasis**

  Atelectasis is a collapse of lung tissue affecting all or part of one lung. Patients must fulfil the following criteria:
  - Clinical symptoms: Shortness of breath, Non-productive cough.
  - Low Oxygen saturations (<92% on Fi02 21%) or Pa02 <8Kpa.
  - CXR or CT scan evidence of atelectasis.
  - Requirement of chest physiotherapy to improve symptoms.
  - Physician diagnosis of atelectasis.

- **Aspiration Pneumonia**

  The following criteria must be fulfilled.
  - Clinical symptoms: Shortness of breath, cough productive of sputum, chest pain in the presence of vomiting or swallowing difficulties.
  - Low Oxygen saturations (<92% on Fi02 21%) or Pa02 <8Kpa.
  - CXR or CT scan evidence of aspiration pneumonia.
  - Physician diagnosis of aspiration pneumonia.

- **Bronchospasm**
  - Clinical symptoms and signs: cough, wheeze and poor air flow.
  - Treatment requiring beta2-agonists.
  - Physician diagnosis of bronchospasm.

- **Pleural Effusion**

  The following criteria must be fulfilled:
  - Clinical symptoms and signs: Shortness of breath, pleuritic chest pain. Stony dullness to percussion or reduced air entry on affected side.
  - Low Oxygen saturations (<92% on Fi02 21%) or Pa02 <8Kpa.
  - CXR or CT scan evidence of pleural effusion.

- Treatment requiring drainage of effusion.

CARDIAC

- **Arrhythmia**
  - ECG changes indicative of new onset cardiac arrhythmia.
  - Requiring medical management or cardioversion of arrhythmias
- **Myocardial Infarction or ischaemia**
  - ECG changes indicative of acute myocardial infarction (MI)
    - ST elevation >1mm in two or more contiguous leads
    - New left bundle branch block
    - New Q wave in two or more contiguous leads
  - Elevation in troponin level indicative of MI
  - Physician diagnosis of MI
- **Cardiac Failure**
  - Cardiac index < 2 litres per m2 (treated first by fluid resuscitation and if no response by inotropic of vasoconstrictive medication)

OTHER

- **Acute Renal Failure**
  - Oliguria of <400ml/24hr.
  - Biochemical derangement of plasma urea and creatinine.
  - Requirement of haemofiltration.
- **Cerebrovascular Accident**
  - Development of an embolic, thrombotic or haemorrhagic vascular accident or stroke with motor, sensory or cognitive dysfunction persisting for more than 24 hrs.
  - Confirmation of CVA on CT head.
- **Sepsis**

  If the patient has two of the following clinical signs and symptoms:
  - Temp>38 or <36.
  - HR >90bpm
  - RR> 20 breaths/min
  - WCC >12 or less < 4

  AND one of the following:
  - Positive blood culture
  - Clinical documentation of source of sepsis.
- **Urinary Tract Infection**

  1) One of the following:

- Temp >38
- Lower urinary tract symptoms (urgency, frequency, dysuria)
- Suprapubic tenderness

AND

- A urine culture of >100,000 colonies/ml urine with no more than two species of organisms

OR

2) Two of the following:
   - Temp >38
   - Lower urinary tract symptoms (urgency, frequency, dysuria)
   - Suprapubic tenderness

AND any of the following:

- Dipstick test positive for leucocytes or nitrates
- Pyuria
- Physician's diagnosis
- Physician institutes appropriate antibiotic treatment.

- **Delirium**
  - Acute confusional state
  - Organically caused decline in cognitive function from a previously attained baseline
  - Fluctuating course
  - Reversible

Appendix 3 – Clavien-Dindo Classification

Table 2: Classification of Surgical Complications - The Clavien-Dindo Classification

Grade		Definition
I		Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II		Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III		Requiring surgical, endoscopic or radiological intervention.
	IIIa	Intervention not under general anaesthesia.
	IIIb	Intervention under general anaesthesia.
IV		Life-threatening complication (including CNS complications)* requiring IC/ICU management.
	IVa	Single organ dysfunction (including dialysis).
	IVb	Multi-organ dysfunction.
V		Death of a patient.

*Brain haemorrhage, ischemic stroke, subarachnoidal bleeding but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit

Appendix 4 – ClassIntra® Classification

Figure 1 Classification of Intra-operative Complications – ClassIntra® v1.0 classification of intraoperative adverse events (iAE)

ClassIntra® v1.0 classification of intraoperative adverse events (iAE). The classification defines iAE as any deviation from the ideal intraoperative course occurring between skin incision and skin closure. Any surgery- and anaesthesia-related event during the index-surgery must be considered and should be rated directly after surgery.[1] A prerequisite is that the indication for surgery and the interventions conform to current guidelines. (BMJ, 2020, author Salome Dell-Kuster *et al.*)

Grade	Definition	Examples
Grade 0	No deviation from the ideal intraoperative course	
Grade I	Any deviation from the ideal intraoperative course • Without the need for any additional treatment or intervention • Patient asymptomatic or mild symptoms	• **Bleeding:** Bleeding above average from small-calibre vessel: self-limiting or definitively manageable without additional treatment than routine coagulation • **Injury:** Minimal serosal intestinal lesion, not requiring any additional treatment • **Cautery:** Small burn of the skin, no treatment necessary • **Arrhythmia:** arrhythmia (e.g. extrasystoles) without relevance
Grade II	Any deviation from the ideal intraoperative course • With the need for any additional minor treatment or intervention • Patient with moderate symptoms, not life-threatening and not leading to permanent disability	• **Bleeding:** Bleeding from medium calibre artery or vein, ligation; use of tranexamic acid • **Injury:** Non-transmural intestinal lesion requiring suture(s) • **Cautery:** Moderate burn requiring non-invasive wound care • **Arrhythmia:** Arrhythmia requiring administration of antiarrhythmic drug, no hemodynamic effect
Grade III	Any deviation from the ideal intraoperative course • With the need for any additional moderate treatment or intervention • Patient with severe symptoms, potentially life-threatening and/or potentially leading to permanent disability	• **Bleeding:** Bleeding from large calibre artery or vein with transient hemodynamic instability, ligation or suture; blood transfusion • **Injury:** Transmural intestinal lesion requiring segmental resection • **Cautery:** Severe burn requiring surgical debridement • **Arrhythmia:** Arrhythmia requiring administration of antiarrhythmic drug, transient hemodynamic effect
Grade IV	Any deviation from the ideal intraoperative course • With the need for any additional major and urgent treatment or intervention • Patient with life-threatening symptoms and/or leading to permanent disability	• **Bleeding:** Life-threatening bleeding with splenectomy; massive blood transfusion; ICU stay • **Injury:** Injury of central artery or vein requiring extended intestinal resection • **Cautery:** Life-threatening burn injury by cautery leading to fire requiring ICU treatment • **Arrhythmia:** Arrhythmia requiring electroconversion, defibrillation or admission to the ICU
Grade V	Any deviation from the ideal intraoperative course • With intraoperative death of the patient	

[1] The following events are not defined as intraoperative adverse events: sequelae, failures of cure, events related to the underlying disease, wrong-site or wrong-patient surgery or errors in indication

Appendix 5 - SWAT Protocol: Infographic Study Within the LaCeS2 Trial (part of the Optimising Recruitment Strategies in the Emergency Setting SWAT, see section 23.2 OPTIMISING RECRUITMENT STRATEGIES IN THE EMERGENCY SETTING)

Sustained recruitment of patients at an anticipated rate is crucial to the successful delivery of randomised clinical trials (1). Various reviews suggested that achieving the required sample size remains a constant challenge for nearly half of randomised trials (2-4). Particularly, emergency surgery trials struggle to recruit participants due to the serious nature of the medical condition as well as the complex demands of the setting. The reduced time between approaching eligible patients and randomisation, and clinician and patient equipoise also add to these challenges.

Infographics are known to have helped in improving patient knowledge in relation to discharge instructions, and statistical association of cancer risk and old age (5) (6). Infographics provide key trial information in a graphical format, so can be easier to understand than text, especially in stressful situations, and by those with lower literacy levels. A study by Buljan and colleagues showed that study participants preferred an infographic to a text-based plain language summary and this was associated with a more positive reader experience and perceived user-friendliness of the information sheet (7). These findings demonstrate the potential benefits of infographics in making randomised trials accessible for patients, and allowing patients to make an informed decision about trial involvement.

We plan to run a Study Within A Trial (SWAT) during the LaCeS2 recruitment period. The objective of this SWAT is to try to maximise efficiency in patient recruitment using an Infographic Sheet (visual document explaining the study). LaCeS2 sites will be randomised to receive the Infographic Sheet plus the standard Patient Information Sheet (PIS) versus a standard PIS only.

The sample size is constrained by the number of potential participants approached and recruitment into the host trial, hence a formal power calculation to determine the sample size has not been conducted.

SWAT study design

The embedded SWAT study design will be a cluster trial; randomisation will be carried out at the site level to reduce cross contamination.

The sample size will be dependent on the LaCeS2 host trial. The LaCeS feasibility trial had an overall mean steady-state recruitment rate at 1.2 patients per month per site, and a more conservative recruitment rate of 0.65 patients per site per month is expected for the LaCeS2 trial. All sites will be approached to take part in the SWAT. The intervention is a recruitment infographic which includes visual information about the purpose of the trial, treatments options, risks and benefits of treatment options, and the randomisation process.

The primary outcome of this embedded SWAT study will be on the recruitment rate to the trial and it will not affect the host-study results. Eligible participants will not be aware of the SWAT, but staff will be aware of the addition of the infographic. The SWAT infographic has been designed in collaboration with two patient representatives on the trial committee and will be submitted to an ethics committee for ethical approval prior to use.

SWAT data analysis

The hypothesis that the use of the infographic will help in increasing the recruitment rate into the host trial will be analysed quantitatively at the end of the study by evaluating recruitment rates and we may also qualitatively assess the implementation and acceptability of the infographic through other aspects of the embedded qualitative work.

SWAT study output

The results of this SWAT will contribute to the evidence about the recruitment strategy of using infographics in clinical and academic research.

References:

1. Briel M, Elger BS, McLennan S, Schandelmaier S, von Elm E, Satalkar P. Exploring reasons for recruitment failure in clinical trials: a qualitative study with clinical trial stakeholders in Switzerland, Germany, and Canada. Trials. 2021;22(1):844.

2. McDonald AM, Knight RC, Campbell MK, Entwistle VA, Grant AM, Cook JA, et al. What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. Trials 2006; 7: 9.

3. Sully BGO, Julious SA, Nicholl J. A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded. Trials 2013; 14: 166.

4. Walters SJ, Bonacho Dos Anjos Henriques-Cadby I, Bortolami O, Flight L, Hind D, Jacques RM, et al. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. BMJ Open 2017; 7(3): e015276

5. Hill B, Perri-Moore S, Kuang J, Bray BE, Ngo L, Doig A, et al. Automated pictographic illustration of discharge instructions with Glyph: impact on patient recall and satisfaction. Journal of the American Medical Informatics Association 2016; 23(6): 1136-42.

6. McCrorie AD, Chen JJ, Weller R, McGlade KJ, Donnelly C. Trial of infographics in Northern

Ireland (TINI): Preliminary evaluation and results of a randomized controlled trial comparing infographics with text. Cogent Medicine 2018; 5(1): 1483591.

7. Buljan I, Malički M, Wager E, Puljak L, Hren D, Kellie F, et al. No difference in knowledge

obtained from infographic or plain language summary of a Cochrane systematic review: three randomized controlled trials. Journal of Clinical Epidemiology 2018; 97: 86-94.

8. Harji D, Marshall H, Gordon K, Twiddy M, Pullan A, Meads D, et al. Laparoscopic *versus* open colorectal surgery in the acute setting (LaCeS trial): a multicentre randomized feasibility trial. British Journal of Surgery 2020; 107(12): 1595-04

26 REFERENCES

1. *National Emergency Laparotomy Audit. National Emergency Laparotomy Audit Report 2018.* https://www.nela.org.uk/reports.
2. Tengberg, L.T., et al., *Complications after emergency laparotomy beyond the immediate postoperative period - a retrospective, observational cohort study of 1139 patients.* Anaesthesia, 2017. **72**(3): p. 309-316.
3. Tolstrup, M.B., S.K. Watt, and I. Gögenur, *Morbidity and mortality rates after emergency abdominal surgery: an analysis of 4346 patients scheduled for emergency laparotomy or laparoscopy.* Langenbecks Arch Surg, 2017. **402**(4): p. 615-623.
4. Harji, D.P., et al., *Systematic review of emergency laparoscopic colorectal resection.* Br J Surg, 2014. **101**(1): p. e126-33.
5. Chand, M., et al., *Systematic review of emergent laparoscopic colorectal surgery for benign and malignant disease.* World J Gastroenterol, 2014. **20**(45): p. 16956-63.
6. Agresta, F., et al., *Current status of laparoscopic colorectal surgery in the emergency setting.* Updates Surg, 2016. **68**(1): p. 47-52.
7. Binda, G.A., et al., *Primary anastomosis vs nonrestorative resection for perforated diverticulitis with peritonitis: a prematurely terminated randomized controlled trial.* Colorectal Dis, 2012. **14**(11): p. 1403-10.
8. Oberkofler, C.E., et al., *A multicenter randomized clinical trial of primary anastomosis or Hartmann's procedure for perforated left colonic diverticulitis with purulent or fecal peritonitis.* Ann Surg, 2012. **256**(5): p. 819-26; discussion 826-7.
9. Vennix, S., et al., *Laparoscopic peritoneal lavage or sigmoidectomy for perforated diverticulitis with purulent peritonitis: a multicentre, parallel-group, randomised, open-label trial.* Lancet, 2015. **386**(10000): p. 1269-1277.
10. Harji, D., et al., *Feasibility of a multicentre, randomised controlled trial of laparoscopic versus open colorectal surgery in the acute setting: the LaCeS feasibility trial protocol.* BMJ Open, 2018. **8**(2): p. e018618.
11. Harji, D.P., et al., *Laparoscopic versus open colorectal surgery in the acute setting (LaCeS trial): a multicentre randomized feasibility trial.* Br J Surg, 2020.
12. https://www.acpgbi.org.uk/news/who-should-perform-colorectal-cancer-resections/.
13. Eypasch, E., et al., *Gastrointestinal Quality of Life Index: development, validation and application of a new instrument.* Br J Surg, 1995. **82**(2): p. 216-22.
14. Eypasch, E., et al., *[The Gastrointestinal Quality of Life Index. A clinical index for measuring patient status in gastroenterologic surgery].* Chirurg, 1993. **64**(4): p. 264-74.
15. Herdman M, G.C., Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X *Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L).* Qual Life Res., 2011 Dec. **20(10)**: p. 1727-36.
16. Ware, J., Jr., M. Kosinski, and S.D. Keller, *A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity.* Med Care, 1996. **34**(3): p. 220-33.
17. Jenkinson, C., et al., *A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies?* J Public Health Med, 1997. **19**(2): p. 179-86.
18. Jenkinson, C. and R. Layte, *Development and testing of the UK SF-12 (short form health survey).* J Health Serv Res Policy, 1997. **2**(1): p. 14-8.
19. Dell-Kuster, S., et. al, *Prospective validation of classification of intraoperative adverse events (ClassIntra): international, multicentre cohort study.* BMJ2020;370:m2917, http://dx.doi.org/10.1136/bmj.m2917
20. Dindo, D., N. Demartines, and P.A. Clavien, *Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey.* Ann Surg, 2004. **240**(2): p. 205-13.

21. Clavien, P.A., et al., *The Clavien-Dindo classification of surgical complications: five-year experience.* Ann Surg, 2009. **250**(2): p. 187-96.
22. Slankamenac, K., et al., *The comprehensive complication index: a novel continuous scale to measure surgical morbidity.* Ann Surg, 2013. **258**(1): p. 1-7.
23. van Dijkum, E.J.M.N., et al., *Validation of the gastrointestinal quality of life index for patients with potentially operable periampullary carcinoma.* 2000. **87**(1): p. 110-115.
24. Machnicki, G., et al., *Gastrointestinal (GI)-Specific patient reported outcomes instruments differentiate between renal transplant patients with or without GI symptoms: results from a South American cohort.* Health and Quality of Life Outcomes, 2008. **6**(1): p. 53.
25. Clavien, P.A., J.R. Sanabria, and S.M. Strasberg, *Proposed classification of complications of surgery with examples of utility in cholecystectomy.* Surgery, 1992. **111**(5): p. 518-26.
26. Slankamenac, K., et al., *The Comprehensive Complication Index: A Novel and More Sensitive Endpoint for Assessing Outcome and Reducing Sample Size in Randomized Controlled Trials.* 2014. **260**(5): p. 757-763.
27. van Bree SH, B.W., Hollmann MW, Zwinderman AH, Matteoli G, El Temna S et al. , *Identification of clinical outcome measures for recovery of gastrointestinal motility in postoperative ileus* Ann Surg 2014. **259** p. 708–714.
28. Gamble, C., et al., *Guidelines for the Content of Statistical Analysis Plans in Clinical Trials.* Jama, 2017. **318**(23): p. 2337-2343.
29. *CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts.* 2017. **167**(1): p. 40-47.
30. Schulz, K.F., D.G. Altman, and D. Moher, *CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials.* 2010. **340**: p. c332.
31. Harji, D., Marshall, H., Gordon, K., Twiddy, M., Pullan, A., Meads, D., …Brown, J., *Laparoscopic versus Open Colorectal Surgery in the Acute Setting (LaCeS Trial): A multicentre, randomised controlled feasibility trial. .* British journal of surgery,, (in press).
32. Excellence, N.I.f.H.a.C. *Guide to the methods of technology appraisal 2013: process and methods (PMG9).* 2013; https://www.nice.org.uk/process/pmg9/chapter/foreword46
33. Drummond MF, S.M., Claxton K, Stoddart GL, Torrance GW., *Methods for the economic evaluation of health care programmes.* Oxford University Press, 2015 Sep 25.
34. Van Hout B, J.M., Feng YS, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard AS, *Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets* Value in health. , 2012 Jul. **1;15(5)**: p. 708-15.
35. https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l.
36. https://euroqol.org/new-eq-5d-5l-valuation-study-for-england-to-be-undertaken-by-euroqol-in-collaboration-with-nice-and-the-department-of-health-and-social-care-and-nhs-england/
37. Brazier JE, R.J., *The estimation of a preference-based measure of health from the SF-12.* Medical Care 2004 Sep. **1**: p. 851-9.
38. Gomes M, N.E., Grieve R, Nixon R, Carpenter J, Thompson SG., *Developing appropriate methods for cost-effectiveness analysis of cluster randomized trials.* Medical Decision Making, 2012 Mar;. **32(2)**: p. 350-61.
39. Faria, R., Gomes, M., Epstein, D., & White, I. R. , *A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials.* Pharmacoeconomics, 2014. **32(12)**: p. 1157-1170.
40. Leurent B, G.M., Faria R, Morris S, Grieve R, Carpenter JR. , *Sensitivity analysis for not-at-random missing data in trial-based cost-effectiveness analysis: a tutorial.* PharmacoEconomics, 2018 Aug **1;36(8)**: p. 889-901.

41. Caro JJ, B.A., Siebert U, Kuntz KM. Medical Decision Making, *Modeling good research practices—overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–1.* 2012 Sep. **32(5)**: p. 667-77.
42. de Verteuil RM, H.R., Vale L; Aberdeen Health Technology Assessment Group, *Economic evaluation of laparoscopic surgery for colorectal cancer.* Int J Technol Assess Health Care, 2007 Fall. **23(4)**: p. 464-72.
43. Barton GR, B.A., Fenwick EA. , *Optimal cost-effectiveness decisions: the role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfection information (EVPI).* Value in health, 2008. **11**: p. 886-97.
44. https://www.nice.org.uk/news/article/nice-announces-details-of-health-technology-evaluation-methods-review.
45. Husereau D, D.M., Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E, CHEERS Task Force., *Consolidated health economic evaluation reporting standards (CHEERS) statement. Cost Effectiveness and Resource Allocation.* 2013 Dec. **1;11(1)**: p. 6.
46. Donovan, J.L., et al., *Development of a complex intervention improved randomization and informed consent in a randomized controlled trial.* J Clin Epidemiol, 2009. **62(1)**: p. 29-36.
47. Paramasivan, S., et al., *Key issues in recruitment to randomised controlled trials with very different interventions: a qualitative investigation of recruitment to the SPARE trial (CRUK/07/011).* Trials, 2011. **12**: p. 78.
48. Donovan, J.L., et al. Journal of Clinical Epidemiology, *The intellectual challenges and emotional consequences of equipoise contributed to the fragility of recruitment in six randomized controlled trials.* 2014. **67(8)**: p. 912-920.
49. Paramasivan, S., et al. , *Enabling recruitment success in bariatric surgical trials: pilot phase of the By-Band-Sleeve study.* Int J Obes (Lond) 2017. **41(11)**: p. 1654-1661.
50. Mills, N., et al., *Training health professionals to recruit into challenging randomized controlled trials improved confidence: the development of the QuinteT randomized controlled trial recruitment training intervention.* J Clin Epidemiol 2018. **95**: p. 34-44.
51. Hughes-Morley, A., et al., *What can we learn from trial decliners about improving recruitment? Qualitative study.* Trials, 2016. **17(1)**: p. 494.
52. Braun, V. and V. Clarke, *Using thematic analysis in psychology.* Qualitative Research in Psychology, 2006. **3**(2): p. 77-101.