**Title: Laparoscopic versus Open Colorectal Surgery in the Acute Setting (LaCeS Trial): A multicentre, randomised controlled feasibility trial.**

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**Abstract**

**Background**

Approximately 30,000 people per annum undergo major, emergency abdominal, gastrointestinal surgery, of which 36% (~10,800) are carried out for emergency colorectal pathology. Approximately 14% of all patients requiring emergency surgery undergo laparoscopic surgery.

**Aims**

The aims of the LaCeS feasibility trial (Laparoscopic versus Open Colorectal Surgery in the Acute Setting) were to assess the feasibility, safety and acceptability of performing a large-scale definitive phase III randomised controlled trial with a comparison of emergency laparoscopic with open surgery for acute colorectal pathology.

**Methods**

LaCeS was designed as a prospective, multicentre, single blind, parallel group, pragmatic, randomised controlled feasibility trial with an integrated qualitative study. Randomisation was performed centrally with patients being randomised on a 1:1 basis between laparoscopic or open surgery.

**Results**

A total of 64 patients were recruited across 5 centres. The overall average steady state recruitment rate was 1.2 patients/month. Baseline compliance for clinical and HrQoL data was 99.8% and 93.8% respectively. The conversion rate from laparoscopic to open surgery was 39.4% (95% CI 22.9% – 57.9%). The 30 day post-operative complication rate was 27.3% (95% CI 13.3- 45.5) in the laparoscopic arm and 41.9% (95% CI 24.6 – 60.9) in the open arm.

**Discussion**

The LaCeS feasibility trial has demonstrated that it is possible to evaluate laparoscopic surgery in the emergency colorectal setting within the context of a randomised controlled trial. LaCeS has demonstrated that it is possible to recruit to a surgical trial in the emergency setting, with good compliance to trial procedures and processes, and overall acceptability by patients and clinicians. The safety data obtained for laparoscopic emergency colorectal surgery indicate an acceptable safety profile, particularly when considering it to that observed in the open arm.

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**Background**

The National Emergency Laparotomy Audit (NELA) reports approximately 30,000 people per annum undergo major, abdominal, gastrointestinal surgery, of which 36% (~10,800) are carried out for emergency 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, with reported rates of post-operative morbidity and mortality of 33-71% and 14-17%, respectively (2, 3).

A number of initiatives have launched over the last decade to improve outcomes in patients undergoing emergency laparotomy, including the use of peri-operative bundles to identify high-risk patients (4, 5), timely management of sepsis and delivery of consultant-led services. Surgeons have started to explore the possibility of adopting a laparoscopic approach in the emergency setting (6). The hypothesis being that the reduced physiological insult associated with laparoscopic surgery will have similar benefits in the emergency setting as that previously seen in the elective setting, leading to reduced pain, earlier recovery and shorter length of hospital stay. The current evidence base informing the use of laparoscopic surgery in the emergency colorectal setting is weak, being limited to a small number of population-based registries and retrospective cohort studies (7-9). Although initial reports indicate benefits of laparoscopic surgery in the emergency colorectal setting, the findings are not uniform across a highly selected patient population consisting of younger and physiologically fitter patients (7). There is a lack of transparent outcome reporting with missing data on complications, re-operation rates and mortality. In a systematic review of 39 studies, Agresta et al concluded that the current evidence for emergency laparoscopic colorectal surgery was 'early, controversial and focused on short term outcomes'(9). The lack of confirmatory data regarding the benefits of emergency laparoscopic colorectal surgery has in part led to the lack of adoption in clinical practice, with NELA reporting static rates of emergency laparoscopic surgery of ~14% over the last 3 years (1).

Surgical trials are associated with a number of practical and methodological challenges, which include difficulties in randomisation, lack of equipoise (10) and variability in experience and delivery of surgical interventions. Surgical trials in the emergency setting add an additional layer of complexity given the time constraints associated with delivering definitive treatment and balancing this against trial-related processes including consent and recruitment. A number of surgical trials have closed early in the emergency colorectal setting due to either poor recruitment rates (11) (12) or a higher than anticipated rate of adverse events (13). Given these recognised difficulties, a feasibility trial investigating emergency laparoscopic colorectal surgery was conducted. The aims of the LaCeS feasibility trial (Laparoscopic versus Open Colorectal Surgery in the Acute Setting) were to assess the feasibility, safety and acceptability of performing a large-scale definitive phase

III randomised controlled trial with a comparison of emergency laparoscopic with open surgery for acute colorectal pathology.

## Methods

### Design

LaCeS was designed as a prospective, multicentre, single blind, parallel group, pragmatic, randomised controlled feasibility trial with an integrated qualitative study. The LaCeS feasibility trial protocol has been published previously (14). The LaCeS feasibility trial is approved by the Yorkshire and The Humber Research Ethics Committee (REC reference: 15/YH/0542).

Patients were recruited from five NHS trusts across the UK. All participating sites had dedicated emergency surgery services with appropriate provisions and expertise to conduct laparoscopic surgery. Randomisation was performed centrally with patients being randomised on a 1:1 basis between laparoscopic or open surgery using minimisation incorporating a random element, stratified by intended consultant surgeon, patient age, body mass index (BMI), American Society of Anesthesiologists (ASA) status, nature of underlying pathology and intended surgical procedure. Patients were blinded to treatment allocation for up to 7 days post-operatively, or until the day of discharge if earlier.

### Eligibility

Patient inclusion criteria included: age ≥18 years old, acute colorectal pathology requiring resectional surgery, a National Confidential Enquiry into Patient Outcome and Death (NCEPOD) classification of urgent requiring surgery between 2-6 hours (Classification 2A) or 6-18 hours (Classification 2B), suitability for both laparoscopic and open surgery, and ability to either provide written informed consent or use of a personal consultee to provide advice on participation in the case of temporary impairment in capacity. Patient exclusion criteria included: haemodynamic instability requiring inotropic support, acute non-colorectal pathology, hand-assisted laparoscopic surgery, laparoscopy and peritoneal lavage alone for colorectal pathology, insertion of an endoscopic stent as a bridge to surgery, pregnancy, pre-existing cognitive impairment, and participation in another surgical trial. Surgeon eligibility criteria included: a minimum of 50 previously performed laparoscopic

colorectal resections, with an annual rate of at least 20 elective laparoscopic resections, with equivalent experience in the open setting.

**Treatment**

Peri-operative treatment of patients was as per institutional protocol. Laparoscopic surgery included the use of multi-port and single-port incisions to establish pneumoperitoneum and facilitate surgical resection. Conversion to open was defined as the use of a midline laparotomy wound for any part of the colorectal dissection. The use of a midline wound to facilitate specimen extraction was permissible. Open surgery was performed through a standard midline laparotomy.

**Outcome Assessment**

A mixed-methods approach was employed to assess recruitment, feasibility and acceptability of the trial, and also the safety profile of laparoscopic surgery in the acute setting as described:

- ***Recruitment***

The primary outcome measure of the LaCeS trial was the overall recruitment rate, with an anticipated recruitment rate of one patient per centre per month. Total numbers of screened, eligible and randomised patients were examined to identify the total available population pool for inclusion into a future phase III trial. Qualitative data were gathered to assess both the practicalities of recruitment and randomisation in the emergency setting.

- ***Feasibility and acceptability of trial processes***

The feasibility of data collection was examined, including the collection of patient and disease characteristics, operative data, pain, health-related quality of life (HrQoL), health care resource use, post-operative morbidity and mortality data, re-operation and re-admission data. Patient-reported generic HrQoL was measured using the SF-12® questionnaire (15) and EQ-5D-5L™(16), whilst disease specific HrQoL was measured using the Gastrointestinal Quality of Life Index (GIQLI) (17). Patient-reported pain was measured using an adapted version of the Brief Pain Inventory (BPI) (18). Health care resource use was captured using clinician completed

procedure and discharge forms, which captured procedure staffing, assessments conducted, imaging, medications and length of stay. Patient completed forms captured use of primary and secondary care. Data were collected on paper by clinicians, trainees and research nurses and uploaded centrally to the clinical trials unit (CTRU).

The feasibility of longitudinal clinical and patient-reported data collection were assessed at baseline, 7 days, 30 days, 3, 6 and 12 months (the latter using a subset of patients) post-operatively. Patient questionnaires were completed in hospital; baseline questionnaires were completed prior to randomisation. Data compliance was calculated for each of these time points as the proportion of completed case report forms (CRFs) or HrQoL questionnaires returned to the CTRU.

The Bang Blinding Index was used to assess the success of blinding (19). When calculated the index takes values between -1 to 1; 1 indicates a complete lack of blinding, 0 is consistent with perfect blinding and -1 indicates opposite guessing which may be related to unblinding.

The acceptability of trial processes and follow up were assessed using in-depth qualitative interviews with clinicians and patients(14). All interviews were informed by a topic guide and were audio-recorded and transcribed verbatim. Qualitative data were analysed using the principles of thematic analysis (20) in NVivo (21). Data were coded independently by two qualitative researchers for emerging themes. Codes and themes were compared and contrasted between the two researchers and any discrepancies were resolved by consensus.

- ***Safety***

The safety of laparoscopic emergency colorectal surgery was assessed by measuring intra-operative and post-operative complication and mortality rates. Patient safety indicators (PSI) as defined by the Agency for Healthcare Research and Quality were also collected. PSIs are a measure of adverse events that patients experience as a result of exposure to the health care system. Intra-operative conversion rates were also measured.

**Endpoint evaluation**

Endpoint evaluation was carried out to establish optimal outcome measures and their timings to inform the design of a large-scale, definitive trial. Qualitative interviews explored a range of clinical and patient-reported outcomes to identify which endpoint will be of most meaning and value to clinicians and patients as a primary endpoint for a definitive trial. Candidate endpoints were analysed quantitatively for completion rates and estimation of variability to help inform future power calculations.

**Sample size**

The target sample size of at least 66 participants was determined to allow precise estimation of parameters of interest according to published recommendations (22) and accounting for a 10% attrition rate. In addition, this sample size allows the estimation of morbidity and mortality rates in the laparoscopic arm with 95% 2-sided confidence intervals (CI) of at most ±17%, allowing its safety profile to be demonstrated. Achieving this recruitment target from five centres over a 15 month period also allows pragmatic estimation of the recruitment rate for a definitive, phase III trial, as well as demonstrating feasibility.

**Statistical Analysis**

No endpoints were subjected to formal statistical testing as no statistical hypotheses were proposed or powered. Data were summarised descriptively using appropriate frequencies and summary statistics, estimating levels of variability using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Data summaries included all randomised patients according to the intervention received.

**Results**

***Recruitment and Patient Characteristics***

Patients were recruited from two teaching hospitals and three district general hospitals across the UK; with four sites providing emergency general surgery services and one site providing a dedicated colorectal emergency surgery service. Thirteen surgeons recruited patients across all sites between July 2016 and November 2017. According to the NELA dataset, 564 patients were identified as undergoing emergency colorectal resection across the five trial sites during the recruitment period. A total of 119 patients were screened and were assessed for eligibility, of which 94 (79.0%) patients were considered eligible and 72 (76.6% of 94 considered eligible)

patients were approached to participate in the trial. A total of 64 (53.8% of 119 screened; 88.9% of 72 approached) patients were randomised; 33 to laparoscopic surgery and 31 to open surgery (Figure 1). All patients received their allocated treatment arm. Twenty-five patients were ineligible for inclusion into the trial (Figure 1). Eight patients declined participation in the trial (Figure 1). Twenty-two screened patients were not approached by the research teams; the most common reason for this was the lack of a randomising consultant on call.

The overall average steady state recruitment rate was 1.2 patients/month per site. The steady state recruitment rate per site varied between 0.57 – 2.78 patients per month (Figure 2). The overall average steady state recruitment rate was 0.9 patients/month per site when the lead site assumed the rate of the next highest recruiting site.

The baseline characteristics of all randomised patients are tabulated (Table 1). The recruited patient population demonstrates good representation of ages, physiological status and disease types.

Qualitative interviews were conducted with 16 trial patients - six received laparoscopic surgery, three had laparoscopic converted to open surgery and seven received open surgery – and 14 healthcare professionals - eight consultant surgeons, three research nurses and three surgical trainees. Qualitative data identified that the recruitment and randomisation processes were acceptable. Patients were accepting of the trial design and the treatment arms and were willing to be appropriately recruited and randomised. A small proportion of patients did express a treatment preference however, this was not considered to be a barrier to participating in the trial. Barriers to recruitment from a clinical perspective included: lack of complete equipoise, with this being most relevant in younger patients and patients with inflammatory bowel disease; difficulty in addressing and challenging patient treatment preferences; and reluctance to approach acutely unwell patients or patients with a complex clinical diagnosis. Organisational barriers to recruitment were identified as lack of available colorectal surgeons on-call, lack of research nurse support and lack of previous experience in recruiting into trials.

***Feasibility and acceptability of trial processes***

- **Data compliance**

Overall, compliance with collection of clinical and patient-reported HrQoL data at baseline and follow-up was good (Table 2). Baseline compliance for clinical and HrQoL data was 99.8% and 93.8% respectively. Data compliance related to important clinical endpoints including conversion rates, re-operation rates, re-admission rates, patient safety indicators, length of stay, post-operative morbidity and mortality rates, and restoration of gastrointestinal function were all above 95%. Compliance rates for clinical data remained above 90% throughout the follow-up period (Table 2). Compliance rates for the patient-reported HrQoL questionnaires declined during the trial follow-up period to 58.3% at 12 months (Table 2 & Appendix A). Health care resource use data provided by health care professionals was of a high quality and in most cases achieved 100% completion. Patient completed resource use form returns declined over time but were at least 50% at 6 months (Appendix B).

- **Blinding**

A total of eight patients were unblinded during the trial; one patient was unblinded by the anaesthetic team pre-operatively, two patients were informed of their treatment allocation post-operatively, three patients were unblinded during dressing changes and two patients were unblinded prior to filling out the Bang Blinding Index. 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. These results suggest there was a failure to adequately blind patients in both treatments arms.

- **Acceptability of trial processes**

Qualitative interviews conducted with patients identified the trial processes to be acceptable; however, patients felt that the number of questionnaires required to be completed was high. Patients felt the pain questionnaire (Brief Pain Inventory) was irrelevant and not an appropriate assessment measure in the emergency setting. Patients expressed that they would have liked online and paper access to questionnaires. Patients found the process of blinding unnecessary and often, correctly, guessed their treatment allocation. Patients expressed a preference to be told of their treatment allocation immediately post-operatively, as opposed to being blinded for up to 7 days.

Overall, healthcare professionals were accepting of the trial design and trial-related processes. Despite appropriate measures being in place to maintain blinding, including appropriate ward notes, team briefings across all medical and nursing staff and appropriate signage and documentation, surgeons felt that blinding was impractical in the emergency setting. The follow-up processes were deemed to be challenging by the research nurses, as the time points did not always coincide with a natural clinical visit. However, surgeons regarded the time points as important and agreed that the proposed time points were appropriate to ensure all relevant differences between the two treatment arms were appropriately captured. Surgeons agreed that a minimum follow-up period of 12 months was necessary to appropriately evaluate the short- and medium-term outcomes of emergency laparoscopic colorectal surgery.

***Safety***

Overall, the safety data obtained for laparoscopic emergency colorectal surgery indicate an acceptable safety profile. A total of 22 patients experienced a post-operative complication within 30 days; this extended to 25 patients within 90 days (Table 3). There were a total of four deaths during the trial period; one death was within 90 days of surgery.

The conversion rate from laparoscopic to open surgery was 39.4% (95% CI 22.9% – 57.9%), with 13 patients being converted. The decision made to convert was on establishment of pneumoperitoneum in 1 patient, following a period of trial dissection in 11 patients and due to an intra-operative complication in 1 patient.

***Endpoint Evaluation***

Qualitative interviews with patients identified post-operative complications as an important outcome when undergoing emergency surgery. Other important outcomes to patients were HrQoL and post-operative recovery. Surgeons participating in the LaCeS feasibility trial shared this perspective, and considered a reduction in post-operative complications to be an important key outcome in the evaluation of laparoscopic emergency colorectal surgery.

**Discussion**

The LaCeS feasibility trial has demonstrated that it is possible to evaluate laparoscopic surgery and open surgery in the emergency colorectal setting within the context of a randomised controlled trial. LaCeS demonstrates that it is possible to recruit to a surgical trial in the emergency setting, with good compliance to trial procedures and processes, and overall acceptability by patients and clinicians. Our safety data suggests that emergency colorectal laparoscopic surgery has an acceptable safety profile. The observed conversion rate is slightly lower than current clinical practice, with NELA reporting a 47% conversion rate (1), and the observed morbidity rate is similar to current published evidence.

The LaCeS trial is relevant to a significant proportion of patients undergoing emergency surgery, with the NELA dataset identifying a patient population pool of 564 patients who underwent emergency colorectal surgery across the five participating centres during the recruitment. Our screening method captured 119 (21.1%) patients throughout this time period, of which the majority of patients (n=94, 79.0%) were eligible for participation into the trial. This reflects the pragmatic nature of our trial, with our eligibility criteria appropriately reflecting current clinical practice. Our steady state rates of recruitment across participating sites reflect that it is feasible to recruit across a range of hospital types and emergency surgery services, including split subspecialty (upper and lower gastrointestinal surgery) and general surgery on-call rotas. The ability to recruit across a range of hospitals is important to ensure appropriate upscaling to a definitive phase III trial within the NHS, to ensure the generalisability of future results and to enable widespread future implementation of emergency laparoscopic surgery.

Challenges to recruitment in surgical trials are well recognised and include lack of equipoise, the complexity of combining clinical and research activities, lack of training and inability to explore patient treatment preferences (23-25). There is a paucity of well-conducted research into recruitment strategies in the emergency setting (26). Our feasibility work identifies the challenges of recruiting in the emergency setting with difficulties encountered in approaching and recruiting clinically complex patients, challenging patient and surgeon equipoise combined with the time constraints of initiating and delivering definitive treatment. Surgeons participating in our integrated qualitative study felt some of these barriers to recruitment can be overcome with appropriate trial-specific training. The use of qualitative methods to explore recruitment within elective clinical trials are

well documented and have been shown to be effective in identifying challenges in recruitment, proposing appropriate strategies to overcome these challenges and driving training pathways (27, 28). Qualitative initiatives such as QuinteT (qualitative research integrated in trials) (29) and Granule (generating recruiters for randomised trials in surgery) have revolutionised the manner in which surgeons and surgical trainees are trained to approach, recruit and randomise patients. It is clear these are required to explore and maximise recruitment within the emergency setting. We will continue to build on the qualitative work undertaken in the LaCeS feasibility trial to refine our trial design for phase III and to continue exploring recruitment strategies in the emergency setting and developing trial-specific training packages.

Our high rates of baseline compliance for clinical data (99.8%) and for patient-reported HrQoL data (93.8%) demonstrate that it is possible to collect trial related data from an acutely unwell population. The routine collection of patient-reported outcome data in the emergency setting has been previously documented to be of low quality, with poor reporting of baseline data (30). This is coupled with high rates of attrition, with Mason et al reporting 6 week response rates of 48.4% despite an initial baseline compliance rate of 93% amongst 156 patients presenting to emergency general surgery services (31). LaCeS demonstrates that it is possible to collect high volume, good quality clinical and patient-reported outcome data in the emergency setting both at baseline and during follow up. Although we did observe attrition during the follow-up period with regards to HrQoL data, our response rates were much higher than previously reported at all candidate follow up time points (31), with our lowest response rate of 58.3% observed at 12 months. Data from qualitative interviews with patients suggested that the burden of questionnaire completion was high, and there were some questionnaires that were deemed to be irrelevant to their clinical status. It is possible that as patients improved clinically and recovered from surgery, they were less inclined to complete HrQoL questionnaires due to the lack of relevance. The mode of our follow up visits also changed as the trial progressed, with a greater proportion of the later follow up visits being undertaken over the telephone. Research nurses stated this made it more difficult to complete and collect HrQoL data, which may have contributed to our reduced response rates at 6 and 12 months post-operatively. The collection of HrQoL data in the emergency setting therefore requires the use of appropriate, accessible and user-friendly patient reported outcome measures, coupled with a follow up strategy that is relevant and acceptable to patients and clinicians. It is clear from our feasibility trial that the majority of our proposed outcome measures were acceptable to patients however, our follow up strategy requires refining.

Feasibility trials are important in providing sufficient methodological evidence regarding trial design, delivery and justification. The successful delivery of the LaCeS feasibility trial has identified that we are able to recruit in the emergency setting and initiate trial-related processes whilst delivering definitive emergency care in a timely manner. This trial has enabled us to pilot our data collection, blinding and follow up processes, and appropriately assess their efficacy. Employing this approach prior to conducting a large-scale, definitive trial ensures the feasibility of delivery of the definitive trial, the acceptability and appropriate modification of the proposed trial processes. To evaluate the role, efficacy and safety of laparoscopic surgery in the emergency colorectal setting, a further large scale, definitive, phase III, multi-centre, randomised controlled trial is required. The data from the LaCeS feasibility trial demonstrates it is feasible to deliver such a trial comparing laparoscopic with open emergency colorectal resection within the NHS.


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