EAGLE: ESCP sAfe-anastomosis proGramme in colorectaL surgEry

An international, cluster randomised-sequence study of a 'Safe-anastomosis' Quality Improvement Intervention to reduce anastomotic leak following right colectomy and ileocaecal resection

Study Protocol

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FUNDING AND SPONSOR

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Ethicon	Unrestricted educational grant to the European Society of Coloproctology to support development of the online training packages.
European Society of Coloproctology	Direct funding for study conduct.
This is an investigator-initiated and investigator-led study. The funder of the study has no role in study design, data collection, data analysis or data interpretation.	
Sponsor	
The University of Birmingham	Sponsor contact: Birgit Whitman
Contact Details	Research Governance Team University of Birmingham Birmingham, B15 2TT researchgovernance@contacts.bham.ac.uk
Sponsor statement	
As formally delegated by the University of Birmingham, the sponsor confirms approval of this protocol.	
Clinicaltrials.gov	Pending
Sponsor reference number	Pending
Compliance statement This protocol describes the EAGLE study only. The protocol should not be used as a guide for the treatment of patients not taking part in the EAGLE study. The study will be conducted in compliance with the approved protocol, the General Data Protection Regulation (GDPR) and subsequent amendments, and the principles of Good Clinical Practice as defined by the European Good Clinical Practice (GCP) Directive. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.	

EAGLE STUDY OFFICE

James Keatley	Project Manager
Brett Dawson	Data Manager
Institute of Translational Medicine, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT.	eagle@contacts.bham.ac.uk

STUDY MANAGEMENT

Study Management Group			
Dion Morton	Professor of surgery	James Keatley	Project manager
Dmitri Nepogodiev	Research fellow	Charles Knowles	Professor of surgery
Aneel Bhangu	Consultant surgeon	Laura Magill	Senior lecturer
Brett Dawson	Data manager	Tom Pinkney	Professor of surgery
Richard Hooper	Reader in statistics	Mark Potter	Consultant surgeon
Operations Committee		**Education Committee**	
Dion Morton	Professor of surgery	Mark Potter	Consultant surgeon
Dmitri Nepogodiev	Research fellow	James Glasbey	Surgical trainee
Brett Dawson	Data manager	Elizabeth Li	Surgical trainee
Jon Evans	Surgical trainee	Ana Minaya Bravo	Consultant surgeon
James Glasbey	Surgical trainee	Sanjay Chaudhry	Consultant surgeon
Sivesh Kamarajah	Surgical trainee	Matteo Frasson	Consultant surgeon
James Keatley	Project manager	Ionut Negoi	Consultant surgeon
Elizabeth Li	Surgical trainee	Luis Sanchez-Guillen	Consultant surgeon
Siobhan McKay	Surgical trainee	Jasper Stijns	Surgical trainee
Daniel Osei-Bordom	Surgical trainee	Tina Van Loon	Surgical trainee
Mary Venn	Surgical trainee	David Zimmerman	Professor of surgery
Data Management Committee			
James Keatley	Project manager	James Gasbey	Surgical trainee
Rita Perry	Project manager	Omar Omar	Statistician
Brett Dawson	Data manager		

OVERSIGHT COMMITTEES

Study Steering Committee		Data Monitoring Oversight Committee (DMOC)	
Antonino Spinelli	Professor of surgery	David Beard	Professor of musculoskeletal sciences

CHIEF INVESTIGATOR & MEDICAL EXPERT

Dion Morton	Professor of Surgery
Room 31, Fourth Floor Academic Department of Surgery University of Birmingham Heritage Building, Birmingham, B15 2TT	0121-371-8910 dion.morton@uhb.nhs.uk

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

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor. I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

This protocol has been approved by:

Study Name	EAGLE	Protocol Version Number	Version: 1.0
CI Name	Dion Morton	Protocol Version Date	12/08/2019
Study Role	Chief Investigator		
Signature		Date	12/08/2019

STUDY SUMMARY

Title: An international, cluster randomised-sequence study of a 'Safe-anastomosis' Quality Improvement Intervention to reduce anastomotic leak following right colectomy and ileocaecal resection.

Background: Anastomotic leak is a severe, potentially life-threatening complication following right colectomy. Internationally, anastomotic leak occurs after 8% of right colectomies. Prospective cohort data demonstrate that patient selection, intraoperative factors, and technical variation are risk factors for anastomotic leak.

Aim: To assess whether implementation of the European Society of Coloproctology (ESCP) Safe-anastomosis Intervention reduces risk of anastomotic leak up to 30-days following right colectomy.

Design: International, multi-centre, cluster randomised-sequence service improvement study, with the hospital as the cluster. Phased Dog-leg schedule for repeated assessments with 3 randomisation sequences. Meta-analysis of results will be performed from individual dog legs.

Eligibility: Any hospital or surgical unit performing elective and/or emergency colorectal surgery. Adults (age 18 years and above) undergoing right colectomy or ileocaecal resection for any indication are eligible, including elective, expedited or emergency surgery by open, laparoscopic or robotic approaches.

Intervention: Three-component, behavioural change intervention for surgeons, anaesthetists and operating theatre staff, supported by an online learning environment: (1) Pre-operative stratification of patients for risk of anastomotic leak; (2) Harmonisation of technique for formation and assessment of stapled and handsewn ileocolic anastomoses; (3) Implementation of a Safe-anastomosis checklist, completed in-theatre immediately prior to formation of an anastomosis and/or maturation of an ileostomy. All centres will receive the intervention.

Primary Outcome measure*:* 30-day overall anastomotic leak rate, defined as clinical or radiologically detected anastomotic leak or intra-abdominal or pelvic collection.

Sample size**:** Assuming an ICC of 0.05, and that each hospital provides data on 10 patients over a 2-month recruitment period (5 per hospital per month), 333 clusters and 4,440 participants will be required to detect an absolute risk reduction in leak rate from 8.1 to 5.6% (relative risk reduction 30%) with 80% power at the 5% significance level.

PLAIN ENGLISH SUMMARY

When patients undergo bowel surgery, for example for a polyp, bowel cancer or inflammatory bowel disease, a section of the bowel is removed. In most patients the ends of the bowel are then joined back together; this is what surgeons call a bowel 'anastomosis'. Although by this stage of the operation the disease has already been removed, the quality of this join is critical to the outcome of surgery. The most feared complication after surgery by both surgeons and patients alike is a leak from this join (an 'anastomotic leak').

The most common bowel operation for which a join is required is called a right colectomy, which removes the first part of the colon on the right-hand side of the abdomen and then joins the small bowel back to the colon again. We determined in 2015 that the risk of leak from this join internationally is 8.1%; that corresponds to around 1 in 12 patients undergoing this operation. Some patients may die from this complication and others will end up with long-term complications and/or a stoma bag (where the bowel is not joined together, but brought to the skin with effluent collected in a bag).

While previous studies have not shown a single clear cause for anastomosis leaks, it was evident from our own data that there is large global variation in performance (hospital to hospital and country to country). This variation is unacceptable when the consequences are so dire for the patient. Importantly, it suggests that sharing good practice across surgical units could improve patient outcomes.

EAGLE is an international quality improvement programme to share best practice and harmonise procedures for surgeons and the theatre teams so that they might perform the best possible anastomosis for each particular patient. This programme has 3 main approaches: (i) preoperative risk stratification (making sure for each patient that it is safe to join the bowel together); (ii) harmonisation of surgical technique (making the join as good as it can be and checking it carefully after it is created), and (iii) implementation of an intra-operative, anastomosis 'checklist' (focussing the attention of the whole theatre team at this critical stage of the operation). We will use a novel scientific approach to assess the patient benefit that enables not only the quality improvement itself to be delivered to all participating hospitals but also enables collection and analysis of data to measure the effect of these measures. The best way of doing this is to embed our proposed quality improvement into a staggered implementation programme, allowing the effect to be assessed between the centres. The specific methodology proposed introduces the intervention in

a stepwise fashion to all hospitals. By the end, all sites will have implemented the programme. Overall, we hope to reduce the leak rate by 30% from 8.1% to 5.6% in about 4,500 patients.

The European Society of Coloproctology (ESCP) with Birmingham Surgical Trials Consortium and Queen Mary University of London Pragmatic Clinical Trials Unit have developed an international network of hospitals and surgeons to deliver the EAGLE study; a 2015 audit included approximately 1,000 surgeons in 284 hospitals from 39 countries and our network has grown now to about 50 countries. The impact of this study can be ground-breaking not only from the perspective of patient safety and thence quality of life, but also because the methodology proposed could be used to improve and standardise surgical quality for many other operations and processes around surgery in the future, in countries with both well developed and less developed surgical services.

BACKGROUND

Clinical problem

Right hemicolectomy and ileocaecal resection are the most common colonic procedures performed worldwide (excluding appendicectomy) by both general surgeons and specialist colorectal surgeons, in both referral and general hospitals. Collectively termed 'right colectomy', these are performed for malignancy and benign indications including inflammatory bowel disease, trauma and volvulus. Internationally, anastomotic leak affects 8.1% of patients after right colectomy, with leak being associated with a 10-fold increase in the risk of death. Anastomotic leak also reduces cancer-specific survival and increases risk of recurrence in oncological resection, and has profound effects on patients' quality of life following surgery and risk of permanent ostomy formation.

Existing international data

The European Society of Coloproctology (ESCP) has established a diverse international network of surgeons from around the world who have collaborated in multi-centre audit and research studies to benefit patients undergoing colorectal surgery. The 2015 ESCP audit of right colectomy and ileocaecal resection demonstrated an anastomotic leak rate of 8.1%, with significant variation in practice around the formation of the ileocolic anastomosis. A total of 14 different anastomotic configurations were reported, with 9 of these being performed collectively by less than 10% of surgeons. Stapled anastomosis was associated with a higher risk of anastomotic leak than handsewn anastomosis, despite handsewn anastomoses being performed more commonly in high-risk, emergency operations. Multi-variable regression analyses also indicated that surgeon specialism was associated with risk of anastomotic leak; general surgeons had a 1.5-fold risk of leak compared to colorectal surgeons. These data indicate that surgeon training may have a role in risk of anastomotic leak, and that a targeted Quality Improvement Intervention to harmonise practice and reduce variation could lead to significant patient benefit.

STUDY RATIONALE

Need for research

Anastomotic leak has been recognised as a priority research topic by the James Lind Alliance. A comprehensive systematic review and meta-analysis of leak prevention strategies in right colectomy demonstrated a low-quality evidence base to support specific technical and perioperative interventions. Most evidence was based on single-centre observational studies at

high-risk of bias. Where randomised studies have been conducted, their interpretation is limited by explanatory designs under-powering, or a lack of contemporary data. International, pragmatic studies are required to improve the evidence base for anastomosis formation, and benefit patients undergoing right colectomy. The 2019 ESCP Hamburg Declaration emphasized the critical importance of addressing unacceptable variation in anastomotic leak rates by quality improvement. The EAGLE study aims to capture evidence for the beneficial effect of a quality improvement intervention (QII) to address this variation.

Justification of patient population

Right colectomy is the most commonly performed large bowel resection in the world. It is performed for both acute and chronic conditions, across high, middle and low-income settings. Despite the high risk of anastomotic leak demonstrated in ESCP audits, right colectomy is often considered a simpler and lower-risk operation than left colectomy or rectal surgery, and consequently consultants may not always be the lead surgeon; in selected cases trainees may perform this operation independently. Finally, it is performed by specialist colorectal surgeons and general surgeons. This makes right colectomy and ileocaecal resection an ideal target for an international QII focussed of risk stratification, multidisciplinary care and harmonisation of technique.

Rationale for study design

It is essential to rapidly develop high quality evidence to inform change in clinical practice. All hospitals must receive the QII (educational programme) to ensure that the study is attractive for centres to participate. Allowance for phased hospital recruitment is necessary, as site set-up pathways and governance structures will vary internationally.

AIMS & OBJECTIVES

Primary objective

- To determine whether a quality improvement intervention (QII) leads to a clinically-relevant overall reduction in anastomotic leak rate from 8.1 to 5.6% (relative reduction 30%) following right colectomy.

Secondary clinical objectives

- To determine the effect of QII on secondary clinical outcomes within 30 days: reoperation for anastomotic leak; reoperation for any cause; unplanned admission to critical care;

readmission; length of hospital stay; postoperative mortality; rate of ileostomy without anastomosis; rate of defunctioning ileostomy with anastomosis.

- To determine the effect of QII on anastomotic leak rate in pre-defined subgroups of clusters or patients.

Secondary process objectives

- To assess the feasibility of a new study design / methodology for evaluating complex interventions such as surgery. This will be assessed by measuring the total number of participating hospital and countries, attrition rate during study set-up, time taken for study set-up at sites, overall time to complete recruitment of sites and patients to the study.
- To evaluate change in behaviour around anastomotic practice following implementation of the Safe-anastomosis intervention by monitoring the proportions of patients undergoing anastomosis, anastomosis with defunctioning stoma, and defunctioning stoma during the study period.
- To assess adherence to completion of the online Safe-anastomosis educational module and implementation of the Safe-anastomosis checklist within surgical teams.

STUDY DESIGN

Study Design

EAGLE is an international, multicentre, cluster-sequence randomised controlled study evaluating the impact of implementation of the *ESCP Safe-anastomosis Intervention* on anastomotic leak rates following right colectomy.

The intervention will be delivered at hospital-level so randomisation will be by hospital, with outcomes assessed at the individual patient level. To ensure that the study is attractive for potential collaborators to participate, all hospitals will implement the quality improvement programme, including those randomised to only collect pre-intervention data. To prevent baseline data gradually becoming contaminated by prior knowledge of the intervention or other unrelated background changes in patient care, we aim to complete data collection within 12 months.

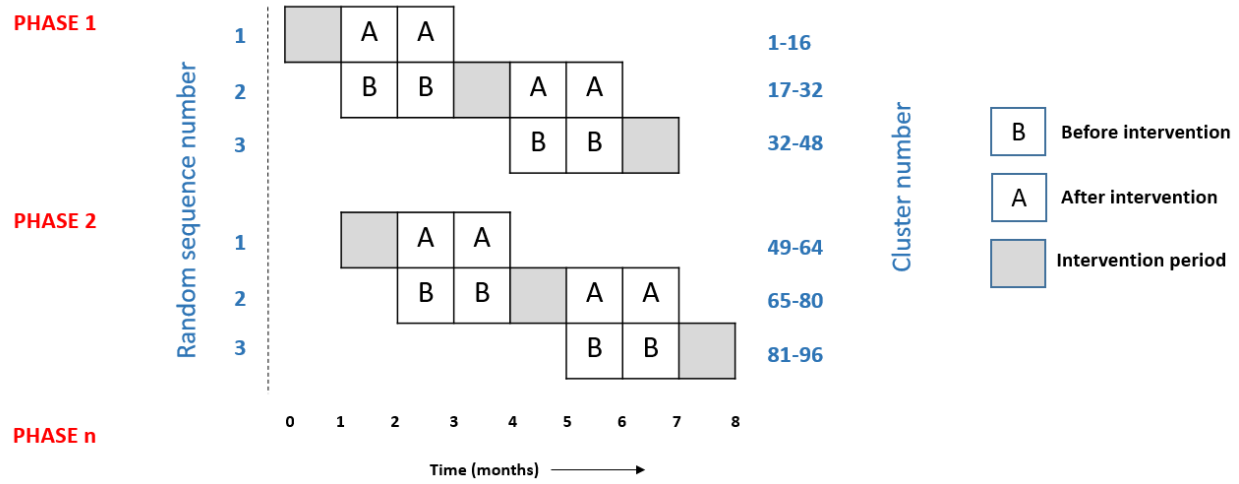

Figure 1: Dog-leg design

The figure shows 2 Dog-leg phases each with 3 randomisation sequences. In the first, 48 hospitals (clusters) are ready to recruit and these are randomised between the 3 sequences. All 3 sequences are eventually exposed to the intervention. Sequence 1 immediately receives the training intervention and data are only collected after the intervention. In sequence 2, data are collected before and after the intervention. The final sequence collects data only before the intervention. The second dogleg commences after the first when more clusters are ready to participate (this is shown as one month on the figure, but can be delayed as practicable). Indicatively, 7 dogleg phases with 48 hospitals (336 hospitals total) each will achieve the sample size required (333 clusters). The timeline for the middle sequence (sequence 2) is shown below. The event rate will be monitored by the DMOC and the sample size reviewed after 50 centres have completed the baseline recruitment.

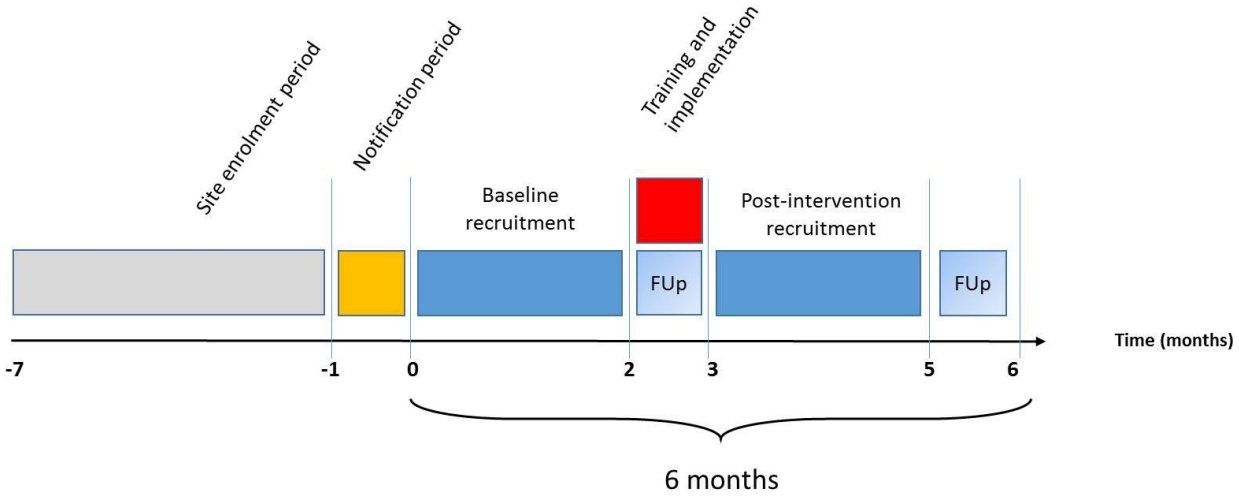

Figure 2: Timeline for site and patient participation

Cluster randomisation

Randomisation of hospitals will be conducted in phases. Within a phase, the available hospitals will be organised into matched triplets according to hospital size (total number of hospital beds) and World Bank country income classification (low, lower middle, upper middle, high income), and whether the hospital accepts referrals from surgeons from at other hospitals of patients needing right colectomy. Within each matched triplet, each hospital will be randomised to a different sequence (three possible randomised sequences).

Co-enrolment

EAGLE permit co-enrolments into other research studies, so long as the study intervention does is not evaluating technical or perioperative interventions where anastomotic leak is the primary outcome measure. The Data Monitoring Oversight Committee (DMOC) will monitor baseline anastomotic leak rates throughout the study period.

ELIGIBILITY

Hospital inclusion criteria

Any hospital or surgical unit performing elective and/or emergency colorectal surgery. There are no restrictions for hospital/unit size or case volume.

Patient inclusion criteria

- All adult patients (age 18 years and above) undergoing right colectomy with or without primary anastomosis. Right colectomy is defined as ileocaecal resection or right hemicolectomy (any colonic transection with the distal resection margin proximal to the splenic flexure).
    - All patients undergoing right colectomy are eligible, including those who do not have an anastomosis and are defunctioned by a proximal stoma.
- Procedures for any pathology, via any operative approach (open, laparoscopic, robotic or converted) are eligible.
- Elective (surgery on a planned admission), expedited, and emergency (surgery on an unplanned admission) procedures are eligible.

Patient exclusion criteria

- Patients undergoing more than one gastrointestinal anastomosis during the same operation.
- In Crohn's disease, additional upstream strictureoplasty or resection/anastomosis to treat disease or strictures at the same operation.
- Simultaneous right colectomy and hyperthermic intraperitoneal chemotherapy (HIPEC) and/or cytoreductive surgery.
- Each individual patient should only be included in EAGLE once. Following the index procedure that is included in EAGLE, patients undergoing additional procedures within the study window should not be included for a second time.

Selection bias

Selection bias will be closely monitored by the Study Management Group. EAGLE coordinators will regularly liaise with site Principal Investigators to ensure that all eligible patients are entered into the EAGLE study. Recruitment rates will be monitored across individual sites and clarification will be sought in case of a drop in recruitment that might indicate that eligible patients were not included. An independent validation process will monitor case ascertainment (see *Monitoring* and *Data Validation,* page 24-25).

PATIENT IDENTIFICATION

Each participating country and hospital will decide how best to identify eligible patients.

Patients can be identified either before, during, or after surgery. As guidance, it is anticipated that patients may be identified from any of the following settings, but that this should preferentially be performed pre-operatively:

- Pre-operatively: surgical outpatient clinics (e.g. when the patient is being booked for elective surgery); planned theatre lists (e.g. at the time of admission for surgery); emergency surgical admissions (e.g. at the time that a decision to operate is made)
- Intra-operatively: by the operating surgical teams during the in-theatre Safe-anastomosis checklist, once the procedure eligibility has been confirmed.
- Post-operatively but before discharge: by either the operating surgeon or by review from the research team.

Patients will be identified by a suitable person who may include:

- The senior operating surgeon
- Any doctor involved in the patients' care (e.g. surgeon in training)
- Research nurse

ETHICS & CONSENT

This study would not be feasible with individual patient randomisation, due to a high risk of bias and contamination between study arms. A cluster randomisation is the most appropriate study design due to the intervention being implemented at hospital-level. Once surgeons have completed the educational module they will implement a change in practice for all subsequent right colectomies they undertake. Once theatre staff are trained to implement the ESCP Safe-anastomosis Checklist, this is likely to become routine practice in the theatre for all right colectomies.

Individual patient consent for the intervention is not possible, as the intervention is being implemented at hospital-level. Moreover, the intervention is low-risk with no specific risks anticipated. Importantly, in this pragmatic study the educational e-modules are intended to inform clinical practice and harmonise care, however, clinical teams will exercise their clinical judgement

and determine appropriate care for each individual patient. Patients will receive usual pre- and post-operative care, which are not affected by the intervention.

Only routinely collected data will be collected in the EAGLE study. Patients will not undergo any additional investigations for the purposes of this study. Clinical follow-up will be limited to review of health records up to a maximum of 30 days postoperatively; there will be no additional patient contact (telephone or in-person) beyond what is normal clinical practice at each centre. As such, if a patient is discharged from hospital before day 30, and no further routine contact with medical services is made, follow-up will be limited to inpatient only. No identifiable data will be collected on the REDCap database; the patient's clinical team will only upload anonymised data.

We anticipate that most ethics review boards will waive the requirement for patient consent, as only anonymised audit data will be collected. However, there may be variation in international regulations and it will be the responsibility of local principal investigators to seek local research ethics committee advice in each participating country to determine whether informed consent should be sought.

BLINDING

The patient will be blinded to their hospital's randomised sequence allocation. Whilst individual patients will be fully informed of the specifics of their surgeons' plans for their operation, they will not be aware whether the ESCP Safe-Anastomosis Intervention has been implemented at the hospital. This reflects routine clinical practice where patients would not typically be aware of specific details of ongoing surgical training programmes.

It is not possible to blind the surgeon or outcome assessor, since the hospital allocation will be known to all members of the clinical team prior to patient recruitment. However, there is an objective primary endpoint (anastomotic leak) and assessors will be trained to collect these data in a standardised manner.

Analysis will be performed blind to allocation sequence (and therefore before and after status) and after data have been cleaned and locked.

PATIENT ENTRY

Once eligibility is confirmed, the CRF should be completed. When the data are uploaded onto the EAGLE REDCap database, a unique REDCap identifier will be allocated to the patient. The

REDCap identifier should be recorded on the CRF. This unique study number will be used in all correspondence between the EAGLE study office and the site.

STUDY INTERVENTIONS

Evidence review

We performed a systematic review of published literature to identify the evidence base for the included interventions. Guidelines, meta-analyses, randomised studies and cohort studies addressing: (1) anastomotic risk stratification; (2) effectiveness of training for standardisation of anastomotic practice; (3) intraoperative checklists, specifically related to formation of anastomosis, were included (date of last search: 01 May 2019).

From 492 initial search results, 16 pre-operative risk scores for prediction of anastomotic leak following colorectal resection were identified. Nine studies reported score performance following internal validation, with AUCs ranging from 0.62 to 0.92. Only 4 scores were externally validated in independent datasets, with AUCs ranging from 0.58 to 0.96. The best performing risk score was the anastomoticleak.com calculator with AUC 0.96. This was externally validated in a small single-centre cohort. No multi-centre studies looking at the effectiveness of training of a standardised anastomotic technique, or intraoperative checklist relating to the formation of a colorectal anastomosis were identified.

Intervention timing

The study intervention will be introduced at a specific timepoint determined by the randomisation sequence. Sites will not be exposed to the study intervention before their allocated timing and this will be ensured by time-locked password access to QII materials.

Intervention details

The EAGLE Safe-anastomosis Quality Improvement Intervention (QII) is a behavioural change intervention composed of three parts:

1. Routine patient-level stratification of risk of anastomotic leak

Calculation of a preoperative risk for each patient undergoing right colectomy or ileocaecal resection using the anastomoticleak.com risk calculator. This includes six factors: Gender; Body Mass Index >30; Anticoagulant use; Intraoperative complication; Serum protein level; Hospital size. Investigators will be trained and encouraged to preoperatively calculate the risk with or without an intraoperative complication. This risk estimate will be used to inform shared decision

making with the patient preoperatively, and will be reviewed in light of intraoperative events as part of the ECSP Safe-anastomosis Checklist.

2. ESCP Safe-anastomosis Checklist

The ESCP Safe-anastomosis Checklist will be implemented in-theatre, immediately prior to the time of formation of an anastomosis or formation of a stoma; this can be before or after transection of the bowel. The checklist should be completed by an unscrubbed member of the theatre team in partnership with the operating surgeon(s), other members of the surgical team, the scrub nurse(s), anaesthetist(s) and operating department practitioner(s).

The Safe-anastomosis checklist (***Appendix 1***) consists of:

(1) Review of any concerns from the anaesthetist, including the anaesthetic risk, haemodynamic instability, vasopressors, blood transfusion, operating time greater than 4 hours, or blood loss greater than 100mls;
(2) Review of any concerns from the surgical team, including the surgeon, scrub staff and operating theatre practitioners. A consensus decision for primary anastomosis (with or without defunctioning enterostomy) or defunctioning enterostomy without anastomosis will be then made by the operating surgeon.
(3) If the consensus decision is to proceed with anastomosis; planning equipment, anastomotic configuration, and delivery of an agreed anastomotic technique, including intra-operative checking of anastomosis integrity.

These four core components are considered mandatory, but adjustment of the checklist to fit into the flow of care at each included centre if permitted. A paper copy of the Safe-anastomosis checklist should be completed and inserted into each participants clinical notes.

3. Harmonised technique for stapled and handsewn anastomosis

A two stage Delphi exercise was undertaken by over 200 specialist colorectal surgeons from around Europe. This has enabled the development of harmonising guidance for surgeons in the absence of high-quality evidence. Such guidance can be amended as new data becomes available. This data has been incorporated into the training platform.

Training platform

The training platform for the study intervention is the ESCP Safe-anastomosis Online Educational Module. This is a secure, password protected Electronic Learning Management System which houses a five-modular educational platform.

(1) **Decision making**, including a pre-operative risk stratification tool for anastomotic leak
(2) **ESCP Safe-anastomosis checklist**, including components and implementation within a theatre team
(3) **Preparing for anastomosis**, including anastomotic healing bowel preparation, choice of stapled versus handsewn anastomoses
(4) **Stapled anastomosis**, including harmonising technique and checking for technical failure.
(5) **Handsewn anastomosis**, including harmonising technique, common variations and checking for technical failure.

It is intended that this educational module should be completed by any providers of colorectal surgical procedures (including consultant/attending surgeons, trainee/resident surgeons, and surgical care practitioners/allied healthcare professionals in surgery) in the one-month implementation period.

A dedicated implementation pack for theatre teams (anaesthetists, scrub nurses, operating theatre practitioners) including an abridged Microsoft PowerPoint Slide set (with translation), Animated video, and in-theatre posters will also be provided. These 'ESCP Safe-anastomosis Theatre Teams' packs will be available across several languages.

VALIDATION OF LEARNING PLATFORM

The training program has been reviewed by the ESCP Education Committee (Chair: Deiter Hahnloser) and revised. It has also been reviewed by the independent Study Steering Committee (Chair: Antonino Spinelli). The platform has been used by 20 international surgeons to ensure language and clarity of meaning is not lost across different cultures.

SAFE-ANASTOMOSIS CHAMPIONS AND TRAINING

The EAGLE study will be led at each site by a surgeon Principal Investigator. This will be a consultant (attending) surgeon who is responsible for the overall conduct of the study. In addition, they will recruit three co-principal investigators who will act as *'Safe-anastomosis champions'* in their centre; this will usually include one surgical trainee, one anaesthetic and one theatre nurse. These site champions will oversee dissemination of training to surgeons, trainees, anaesthetists and theatre staff at their site, and sustainability of implementation of the Safe-anastomosis QII. The *'Safe-anastomosis champions'* will be asked to co-ordinate training days, an in-theatre pilot of the Safe-anastomosis checklist in their local centre, and encourage completion of the online

educational module by all members of the theatre team (e.g. local presentations to research and/or governance meetings).

All surgeons who perform (e.g. electively) or who are likely to perform right colectomy (e.g. whilst on call) will be invited to complete the online educational module. The training modules will be password protected to monitor compliance within the experimental arm, and centre-level completion rates monitored. Once the randomisation sequence requires implementation of the QII, this will be introduced over an implementation period of one month before 'post-implementation' data collection is commenced.

STANDARDISATION OF OTHER SURGICAL PROCESSES

As a pragmatic clinical study, other aspects of the operation, apart from those allocated as part of the education tool, will be determined by the preference of the attending surgeon and anaesthetist, and not be further defined within the *EAGLE Protocol*. Participating centres will be expected to implement the World Health Organisation Surgical Safety Checklist for all participants to standardise perioperative care prior to site opening; the implementation of individual components of this checklist will not be recorded for the purposes of the study. Within this pragmatic study, other anastomotic leak reduction measures may be used at the surgeon's discretion, for example indocyanine-green fluorescence assessment of bowel perfusion. These measures will not be controlled for within the study protocol.

PRIMARY OUTCOME MEASURE

The primary outcome measure is anastomotic leak within 30-days of surgery (with Day 0 as the day of surgery). The denominator for the primary outcome is the total for patients who had a primary anastomosis. The numerator is anastomotic leak, defined as a composite of either:

- Anastomotic leakage identified radiologically or clinically

or

- Intraperitoneal (abdominal or pelvic) fluid collection identified radiologically, as per the Centre for Disease Control Criteria for Organ Space infection

SECONDARY OUTCOME MEASURES

The denominator is the total for patients who had a primary anastomosis:

- Reoperation for anastomotic leak, within 30-days

The denominator is the total for all patients:

- Reoperation for any cause, within 30-days
- Unplanned admission to critical care, within 30 days
- Readmission within 30 days.
- Length of hospital stay, up to 30-days
- Mortality within 30-days.
- Rate of ileostomy without anastomosis.
- Rate of defunctioning ileostomy with anastomosis.

PROCESS EVALUATION

Adherence to the key components of the intervention will be recorded on the Anastomosis Checklist. This will be a printed sheet which is completed by a circulating staff member in theatre. Specifically they will record:

- Whether pre-operative risk stratification was performed.
- Whether intra-operative risk stratification was performed.
- Whether the surgeon participated in the Anastomosis Checklist.

This process will be co-ordinated by the Theatre Nurse co-Principal Investigator. At the end of the operation, the Anastomosis Checklist will be filed in the patient notes. This will subsequently be accessed by the data collection team to extract data to the CRF.

DATA COLLECTION AND FOLLOW-UP

Data will be collected in two phases. During the index admission pre-operative and intra-operative data will be collected. Local Principal Investigators will establish pathways in their hospitals to ensure robust data collection; for example, pre-operative data could be collected on the morning prior to surgery, with intra-operative data fields completed in theatre immediately following completion of the procedure. Alternatively all data could be collected in theatre, or in the post-operative ward.

All patients, including those who did not have a primary anastomosis, will be followed-up to a maximum of 30-days postoperatively (with Day 0 being the day of surgery) by a review of their inpatient health records, routine clinic visit letters, and reports for postoperative radiological investigations arranged as part of normal patient care. There will be no additional patient contact (telephone or in-person) beyond what is normal clinical practice at each centre. The study is designed efficiently so that existing patient follow-up pathways and health records can be used, with only data that is routinely collected as part of normal clinical care being captured.

Most anastomotic leaks following ileocolic anastomosis occur in the early post-operative period (days 4-14). Although a small number of anastomotic leaks occur beyond day 30, limiting follow-up to 30 days will ensure that the vast majority of leaks are captured.

SAMPLE SIZE

Assuming no decay in the intracluster correlation over time, our 2015 data suggest an ICC of approximately 0.05 [REF 2017]. Based on feasibility (below), we assume that each hospital provides data on 10 patients over a 2-month recruitment period (5 per hospital per month). An overall 'design effect' or sample size inflation factor for our cluster-randomised dogleg design relative to an individually randomised parallel groups design can then be calculated. Using this design effect, to detect a 30% relative risk reduction in leak rate from 8.1 to 5.6% with 80% power at the 5% significance level requires 292 clusters and 3,895 patients. In practice there will be variation in recruitment at different hospitals, which can be expected to increase the required sample size. Following a published rule of thumb, we assume that this inflates the sample size by at most 14% leading to a required sample size of 333 clusters and 4,440 patients.

PROJECTED RECRUITMENT

Data for 3,208 right colectomies was submitted by 284 centres over a 2 month period to the 2015 ESCP Right Hemicolectomy Audit; an average of 11.3 patients per 2 months. 81% the sites recruited >10 patients over the 2-month period. A mean of 10 patients per centre is required for each 2 month recruitment period.

Patients per centre (2 months)	Proportion of centres
1-5	19% (n=53)
6-10	37% (n=104)

11-15	22% (n=63)
16-20	14% (n=39)
21-30	6% (n=17)
31+	3% (n=8)

***Table 1**: Patient recruitment data from 2015 ESCP Right Colectomy & Ileocaecal Resection Audit*

STATISTICAL ANALYSIS PLAN

This will be conducted on an intention-to-treat basis i.e. all patients recorded in the database during the scheduled 2-month recruitment periods will be included, and those in the second period will be considered exposed to the intervention regardless of whether learning from the intervention was actually implemented. The primary outcome will be 30-day anastomotic leak rate. In the primary analysis, 30-day leak rate will be modelled using mixed effects logistic regression with random cluster (hospital) effects allowing inclusion of baseline risk factors such as co-morbid disease and ASA score and adjustment for a fixed time effect between time periods.

Planned additional analyses

Pre-planned exploratory sub-group analyses of the primary outcome will be performed in the following groups:

At cluster (hospital) level:

- Number of beds (<500 versus ≥500 total hospital beds).
- Right colectomy volume (<10 patients versus ≥10 patients per 2 month period).
- Early adoption (early versus late study entrants).
- Health service expenditure per capita in purchasing parity (top versus middle versus bottom tertile).
- Proportion of operating surgeons in each centre completing the online training modules prior to 'post-implementation' data collection (high [≥80%], intermediate [50-79%], low [<50%]).
- World Bank income group (high versus middle/low income country).

At patient level:

- Indication for surgery (malignant versus benign, e.g. inflammatory bowel disease).
- Procedure urgency (elective versus expedited/ emergency).
- Age (≤65 years versus >65 years).
- Operative approach (open versus laparoscopic/ robotic).
- Anastomotic technique (stapled versus handsewn anastomosis).
- Primary operating surgeon experience as reported (trainee versus consultant).
- Primary operating surgeon specialism as reported (general versus colorectal surgeon).

Reverse analysis will also be undertaken to explore what are the characteristics of hospitals with a big change versus no change, and do these differ in respect of cluster characteristics.

DATA HANDLING AND RECORD KEEPING

Source Data

Source data within the EAGLE study will be kept as part of the participants' medical notes generated and maintained at site. As all data collected and analysed within the EAGLE study are routinely collected, source data will only be within the medical notes.

Data Management

Information will be collected at the following times:

- During the index hospital admission.
- At 30 days after the operation.

Data will be entered directly onto the secure electronic EAGLE REDCap database by study collaborators at the participating hospital sites.

Site study collaborators will be provided with a paper copy of the eCRF to facilitate data collection. If this is used, they should then transfer data from the paper CRF into the online EAGLE database (https://www.bistc.redcap.bham.ac.uk). EAGLE data management staff will check all incoming data CRFs for completeness, data consistency and compliance with the protocol. If discrepancies or missing data are identified, the EAGLE data management staff will raise queries with the research team at the participating hospital via the EAGLE database.

Data Security and Data Protection

The security of the Study Database System is governed by the policies of the University of Birmingham. The EAGLE study database will be hosted on the REDCap system managed and maintained by the BiSTC.

Data management and data security within the BiSTC will abide by the requirements of the General Data Protection Regulations (GDPR) and any subsequent amendments. The study will be conducted at collaborating sites in accordance with the country-specific data protection requirements. Data will be acquired and stored on the REDCap platform. Access to data will be restricted by usernames and passwords, at participating sites. Each participant will be allocated a unique study number at entry. All communication will use this as the identifier. All data will be analysed and reported in summary format. No individual will be identifiable.

QUALITY CONTROL AND QUALITY ASSURANCE

Site set-up and site initiation

Study collaborators at participating hospitals will undergo a detailed, standardised site set-up training package. The package is formed of multiple components and covers the following areas:

- Online training modules

  This will include modules on the intervention, study set-up, study delivery, and follow-up. Study-specific GCP training will be incorporated throughout these modules.

- Online site initiation visit

  Once a site has completed all set-up process, all team site team members will be invited to attend a teleconference with an EAGLE Coordinator and/or Operations Committee member. This teleconference will cover details regarding the intervention, study delivery, and follow-up.

- Ongoing support

  Each local principal investigator will have ongoing support from an assigned EAGLE Coordinator with at least weekly teleconference or email contact. As the study proceeds EAGLE Coordinators will tailor the content of these weekly contacts to the specific study processes that are relevant at that time.

All training has been CPD-accredited (3 points) by the Royal College of Surgeons of England.

Site training is mandatory and completion of each module by the relevant staff is a prerequisite to site opening to recruitment. The monitoring of completion of training will be undertaken by staff at the EAGLE Study Office.

Prior to opening, all participating local Principal Investigators will sign an Investigator's Agreement with the University of Birmingham to document acceptance of the responsibilities of the PI at the site.

Monitoring

Due to the nature of EAGLE, monitoring will be employed to ensure the credibility of the data. Monitoring will be undertaken centrally and will include, but will not be limited to, monitoring of: protocol adherence; patient selection and minimisation of selection bias; review of data relating to the primary and secondary outcomes. Monitoring will be via data validation and range checks built into the REDCap database used to collect and manage the data; statistical monitoring techniques will be used to compare data from different sites to identify sites that may warrant further investigation, site monitoring and/or support and training. Review by the study oversight committees (SSC, DMOC, SMG) will also include the review of completion of primary and secondary outcomes, adherence to protocol, and selection bias.

EAGLE study staff from UoB will be in regular contact with the site research teams to check on progress and address any queries that they may have.

The EAGLE Data Management Committee will check submitted CRFs from the participating hospitals for compliance with the protocol, data consistency and missing data. They will send participating hospitals data queries for missing data or clarification of inconsistencies or discrepancies.

Data validation

Validation of case ascertainment (the proportion of eligible cases that were included within the EAGLE study) will be undertaken in a random sample of 10% of centres. In those centres data validation will be led by the Theatre Nurse PI. They will review theatre logbooks to is identify all eligible patients who were operated during the centre's data collection window. The Theatre Nurse PI will confirm these patients' eligibility through consultation with an independent surgeon who has not been involved in the initial data collection at that site. The total number of eligible cases at each site will be submitted to the EAGLE Coordinating Office. The total for eligible cases and cases actually submitted to REDCap will be pooled across centres participating in the validation exercise, and the case ascertainment rate will be calculated.

STUDY ORGANISATIONAL STRUCTURE

The EAGLE Study Office (at the University of Birmingham)

The coordinating centre for the EAGLE study is based at the University of Birmingham through the Birmingham Surgical Trials Consortium (BiSTC).

Each site will appoint a local Principal Investigator (PI) who will take responsibility for the study at site. This will be a consultant (attending) surgeon who is responsible for the overall conduct of the study. In addition, they will recruit three co-principal investigators; this will usually include one surgical trainee, one anaesthetic and one theatre nurse. Each site will be mentored by a member of the Eagle Study Management team, who will provide guidance, oversight and support directly to that site on behalf of the SMG.

Sponsor

The University of Birmingham is the Sponsor of the EAGLE study in all collaborating countries. Sponsorship will be provided by the University of Birmingham upon signing of the Study Agreement with each site.

EAGLE Study Management Group

The EAGLE Study Management Group (SMG) includes those individuals responsible for the day-to-day management of the study. This will include the Chief Investigator, EAGLE operations staff, statisticians, and lead clinicians. The group will meet every six weeks to review ongoing progress. The role of the SMG is to monitor all aspects of the conduct and progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard the quality of the study itself.

EAGLE Operations Committee

The EAGLE Operations Committee is chaired by the Chief Investigator. It includes the surgical coordinators responsible for the delivery of the study at sites and EAGLE operations staff.

The group will initially meet on a weekly basis at the start of the study and then two-weekly or monthly as the study progresses, dependent on the needs of the project. The role of the operations group is to recruit investigators and hospitals to the study, and to support study set-up at individual hospitals. The Operations Committee will have weekly contact with all participating centres either by teleconferencing or email to ensure adherence to the study protocol. In view of the large size of the study, the Operations Committee will be supported by a wider pool of EAGLE

Coordinators who will act as an interface between local Principal Investigators and the Operations Committee.

EAGLE Data Committee

The EAGLE Data Committee includes the study statistician and EAGLE operations staff. Access to study databases is restricted to the members of the Data Committee. The Data Committee will liaise closely with the Operations Committee to manage and monitor database access.

Study Steering Committee

The remit of the Study Steering Committee (SSC) is to provide overall supervision of the study and ensure that it is being conducted in accordance with the principles of Good Clinical Practice and other relevant regulations.

The SSC will meet face-to-face or via teleconferencing every three months, or more often if required.

The specific tasks of the SSC are:

- To approve and sign off the study protocol and any protocol amendments.
- To resolve problems brought to it by the EAGLE study management team
- To provide advice to the investigators on all aspects of the study.
- To review recommendations from the DMOC, and help with the decision-making that follows on from the recommendations of the DMOC.

Data Monitoring Oversight Committee

The DMOC is scheduled to meet prior to the study commencing every three months thereafter until the study closes to recruitment. Additional meetings may be called if recruitment is much faster than anticipated and the DMOC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if required.

The DMOC will review data completeness, recruitment per-site, recruitment overall, and protocol deviations. The DMOC will make recommendations to the SSC

Finance

EAGLE is an investigator-initiated and investigator-led study. The EAGLE online training packages have been developed with an unrestricted educational grant from Ethicon. The overall funding for study conduct has been provided by the European Society of Coloproctology.

CONFIDENTIALITY AND DATA PROTECTION

Patient identifiable information will not be collected in this study. All participant data held at the University of Birmingham will be anonymised.

All data collected about participants will be identified using only a unique EAGLE study number. This number will be automatically allocated via REDCap once a new patient record is created in the EAGLE REDCap database.

Any correspondence between the EAGLE study office and hospital sites will use the EAGLE study number only.

The linkage between REDCap study ID and participants will be maintained in strict confidence at participating sites. This data will not be submitted to the EAGLE study office and will not be sent outside of the participating site.

Confidentiality of all participant's data will be maintained and there will be no disclosure of information by which participants may be identified to any third party other than those directly involved in the treatment of the participant.

INSURANCE AND INDEMNITY

The University of Birmingham has in place Clinical Trials indemnity coverage for this study which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the study.

The risk of the trial is no greater than the risk of the standard clinical care. Responsibility for the participants at Sites remains with the organisation responsible for the Clinical Site and it is therefore indemnified through their normal arrangements.

AUTHORSHIP

The output from this research will be published under a single corporate authorship group: "European Society of Coloproctology Safe-anastomosis Collaboration". The following roles will be

recognised within the collaborating authorship list: Writing group, Protocol group, EAGLE Study Management Group, EAGLE Operations Committee, EAGLE Education Committee, EAGLE Data Management Committee, Study Steering Committee, Data Monitoring Committee, Statistical analysis, ESCP Cohort Studies and Audits Committee, ESCP Research Committee, EAGLE co-ordinators, Principal Investigators, co-Principal Investigators, Collaborators. Specifically each participating hospital may include up to seven collaborators: the Principal Investigator, anaesthetic, and theatre nurse co-Principal Investigators; the surgical associate co-Principal Investigator; and three further collaborators supporting study delivery and data collection. An increase in the number of collaborators at a participating hospital is potentially possible but should be prospectively agreed on a case-by-case basis with the EAGLE Operations Committee. All co-authors will be PubMed searchable and citable.

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APPENDIX 1. ESCP Safe-anastomosis Checklist

ESCP SAFE ANASTOMOSIS CHECK LIST

Q1: Are there any concerns from the anaesthetist or theatre team?

- ☐ From the preoperative risk assessment?
- ☐ Due to intra operative haemodynamic instability, need for vasopressors, or need for blood transfusion?
- ☐ Has the operative time been longer than 4 hours, or blood loss greater than 100mls?

Q2: Does the surgical team feel it is appropriate to proceed to anastomosis?

- ☐ What was the calculated preoperative risk of anastomotic leak?
- ☐ Have there been unforeseen surgical events, operative field contamination or technical difficulties during the operation that will influence this risk?
- ☐ Does the patient have the physiological reserve to withstand the adverse effects of anastomotic leak?

Q3: What type of anastomosis is planned?

Stapled

- ☐ Is the bowel being anastomosed healthy?
- ☐ Is the bowel oedematous and/or inflamed?
- ☐ Is there presence of pus?
- ☐ Is there any bowel end ischaemia?
- ☐ Is there any mesenteric torsion?
- ☐ What instruments are required?
- ☐ What stapler size is required?
- ☐ How do you plan to test the anastomosis?

Handsewn

- ☐ Is there any bowel end ischaemia?
- ☐ Is there luminal discrepancy?
- ☐ What anatomical arrangement is planned? (Side to side/end to side/end to end)
- ☐ Which sutures are to be used?
- ☐ Interrupted or continuous
- ☐ One or two layers
- ☐ How do you plan to test the anastomosis?

APPENDIX 2. EAGLE Case Report Form

Local Patient Identifier	*not uploaded to REDCap*	**Unique REDCap Identifier**	
Pre-operative data			
Age (on day of operation)		Years	
Sex		Male / Female	
American Society of Anaesthesiologists (ASA) grade		1 / 2 / 3/ 4/ 5	
Previous abdominal surgery		No / Yes	
History of ischemic heart disease or cerebrovascular disease		No / Yes	
History of diabetes mellitus		No / Yes	
Body Mass Index >30		No / Yes	
Oral anti-coagulants		No / Yes	
Pre-operative total protein level (g/dL) *– nearest 0.5 units*			
Pre-operative haemoglobin (g/dL)			
Procedure indication		Malignancy / Inflammatory bowel disease / Other	
Intra-operative data			
Bowel preparation		None / Mechanical bowel preparation only / Mechanical bowel preparation with oral antibiotics	
Primary operating surgeon		Consultant colorectal surgeon / Trainee colorectal surgeon / Consultant general surgeon / Trainee general surgeon	
Most senior surgeon in theatre		Consultant colorectal surgeon / Trainee colorectal surgeon / Consultant general surgeon / Trainee general surgeon	
Procedure urgency		Elective (planned) / Expedited (within two weeks of decision to operate) / Emergency (unplanned)	
Operative approach		Open, Laparoscopic (completion, conversion to open), Robotic (completion, conversion to open)	
Operative field contamination		Clean-contaminated / Contaminated / Dirty	
Anastomosis formed		Stapled / Handsewn / No anastomosis (end ileostomy formation)	
If yes: Anastomotic configuration		Side-to-side / end-to-side / end-to-end	
If yes: Is there a defunctioning loop ileostomy		No / Yes	
*If yes: W*as the anastomosis tested?		No / Yes -air leak test / Yes - probed with forceps	
If yes: Did the anastomosis require revision?		No / Yes	

Intraoperative complications	Blood loss >1L / Operating time >4h / Solid organ or ureteric injury / Vascular injury / Blood transfusion / Hemodynamic instability / Vasopressor requirement (select all that apply)
Duration of surgery (minutes) *knife-to-skin to completion of skin closure*	1-60 / 61-119/ 120-179/ 180-239/ ≥240
Was an ESCP Safe-anastomosis Checklist completed?	Yes / No
Was anastomotic leak risk calculated **pre-operatively**?	Yes / No
Was anastomotic leak risk calculated **intra-operatively**?	Yes / No
Has the senior surgeon completed the Safe-anastomosis module?	Yes / No
Post-operative data	
Post-operative critical care admission	None / Planned from theatre / Unplanned from theatre / Unplanned from ward
Total length of hospital stay	Days (up to 30 postoperative days)
Anastomotic leak or intra-abdominal/pelvic collection	None / Grade A – requiring no further intervention, radiologically diagnosed / Grade B – requiring radiological reintervention / Grade C – requiring surgical reintervention
If yes: How was the leak diagnosed?	Clinical diagnosis only/ Ultrasound imaging/ CT imaging/ MR imagining/ Intraoperative diagnosis
Re-operation within 30 days	No / Yes
Re-admission within 30 days	No / Yes
Mortality within 30 days	No / Yes