ESCP Safe Anastomosis ProGramme in CoLorectal SurgEry (EAGLE)

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TRIAL PROTOCOL

ESCP Safe Anastomosis ProGramme in CoLorectal SurgEry (EAGLE): Study protocol for an international cluster randomised trial of a quality improvement intervention to reduce anastomotic leak following right colectomy

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Abstract

Aim: Cohort data suggest that anastomotic leak occurs after 8% of right colectomies causing significant morbidity and mortality. Patient selection, intra-operative factors, and technical variation all contribute to risk of leak. The EAGLE study will assess whether implementation of the European Society of Coloproctology (ESCP) Safe Anastomosis Intervention reduces anastomotic leak following right colectomy.

Methods: An international, multi-centre, cluster randomised trial will be undertaken with hospitals as clusters. Hospitals will be recruited in a number of distinct phases, with each phase following the same research plan, in which clusters are randomised to one of three, staggered (dog-leg) schedules for implementation of the Safe Anastomosis Intervention.

Results: Results from different phases will be meta-analysed. The intervention is a three-component behavioural change programme for surgeons, anaesthetists and operating room staff, supported by an online learning environment. All colorectal surgical units around the world will be eligible. Adults undergoing elective or emergency right colectomy or ileocaecal resection, by any approach and for any indication will be included. The primary outcome is 30-day anastomotic leak rate, defined as clinical or radiologically-detected leak or intra-abdominal or pelvic collection. Assuming hospitals provide data for an average of 10 patients per two month recruitment period, 333 clusters (4440 patients in total) will allow for detection of an absolute risk reduction of anastomotic leak from 8.1% to 5.6% (relative risk reduction 30%). This protocol adheres to Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT).

Discussion: The protocol describes the methods for an evaluation of a hospital-level, education-based quality improvement intervention targeted to reduce the life-threatening surgical complication of anastomotic leak.

Statement of adherence to SPIRIT guidelines: This protocol adheres to 2013 Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) checklist [1] and identifies protocol items in {curly brackets}. For administrative information please refer to Table S1. The SPIRIT checklist is attached as Appendix S4.

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[†]See Acknowledgment section for members of ESCP EAGLE Safe Anastomosis Collaborative.

KEYWORDS
anastomotic leak, colorectal surgery, dog-leg cluster randomised, quality improvement study, randomised trial, right hemicolectomy

INTRODUCTION

Anastomotic leak is a serious complication of colonic surgery resulting in significant morbidity and mortality. Right hemicolectomy and ileocaecal resection (collectively termed "right colectomy") are performed for the management of colonic malignancy or benign indications including inflammatory bowel disease, trauma and volvulus. Right colectomy is the most common colonic procedure performed worldwide (excluding appendicectomy) by general and specialist colorectal surgeons in general hospitals and tertiary referral centres. The 2015 European Society of Coloproctology (ESCP) international audit of right hemicolectomy and ileocaecal resection demonstrated an anastomotic leak rate of 8.1% after right colectomy, with an associated 10-fold increased risk of death [2]. Anastomotic leak also reduces cancer-specific survival, increases risk of recurrence in oncological resection, has profound effects on quality of life in patients following surgery and heightens the risk of permanent stoma formation [3,4]. Given the wide variation in leak rates between studies and centres seen globally, we hypothesise that a proportion of anastomotic leaks are avoidable. Strategies to predict patients at high risk of anastomotic breakdown and to optimise operative techniques are required to prevent their serious consequences.

The ESCP audit demonstrated significant variation in practice around the formation of the ileocolic anastomosis with 14 different anastomotic configurations in the study population (nine of which were performed collectively by less than 10% of surgeons) [2,5]. Stapled anastomosis was associated with a higher risk of anastomotic leak than hand-sewn anastomosis, despite more frequent use of hand-sewn anastomoses in higher risk, emergency operations. Multivariable regression analyses also indicated that surgeon specialism was associated with risk of anastomotic leak; general surgeons had a 1.5-fold increased risk of leak compared to colorectal surgeons [5]. These data indicate that surgeon training may have a role in reducing the risk of anastomotic leak, and that a targeted Quality Improvement Intervention (QII) to harmonise practice and reduce variation could lead to significant patient benefit.

Measures to reduce anastomotic leak have been recognised as a priority research topic by patients and public (James Lind Alliance) [6]. This view is shared by surgeons, leading to the 2019 ESCP Hamburg Declaration which emphasised the critical importance of addressing unacceptable variation in anastomotic leak rates by quality improvement [7]. The EAGLE study seeks to deliver this quality improvement and to capture evidence of its effect.

Objectives

Primary objective

- To determine whether the ESCP Safe Anastomosis quality improvement intervention (hereafter QII) leads to a reduction in anastomotic leak rate following right colectomy at 30-days after surgery.

Secondary clinical objectives

- To determine the effect of the QII on other clinical outcomes within 30-days of surgery including:
  a. Reoperation for anastomotic leak
  b. Reoperation for any cause
  c. Unplanned admission to critical care
  d. Readmission to hospital
  e. Postoperative mortality
  f. Length of hospital stay
- To determine the effect of the QII on the rate of stoma formation at index operation for all patients included in the study, either:
  a. Stoma without primary anastomosis, or
  b. Defunctioning ileostomy with primary anastomosis.
- To determine the effect of QII on anastomotic leak rate in predefined subgroups of clusters or patients (see Methods of analysis section).

Secondary process objectives

- To assess the feasibility of recruitment, retention and site set-up in this new study design. We will record the total number of participating hospital and countries, attrition rate during study set-up, time taken for study set-up at sites and to randomisation, and overall time to complete recruitment of sites and patients to the study.
- To assess completion of the QII online training modules and adherence to their components.

Study design

This protocol describes an international, multi-centre, cluster-sequence randomised trial with hospitals as clusters. This design satisfies several key study design requirements: (1) to randomise different hospitals at different time-points, (2) to use data that are routinely available, (3) to minimise burden of data collection, (4) to maximise statistical efficiency, and (5) to ensure that all hospitals are exposed to the QII. These tenets led to the development of a novel study design incorporating several study phases. Each phase will follow the same cluster-randomised plan in which hospitals are randomised to one of three, staggered schedules for implementation in a "dog-leg" design (Figure 1; [8]). Phasing allows a batch of clusters (hospitals) to start once governance approvals are in place while other hospitals are progressing approvals to avoid delays. The

individual phases (which are underpowered alone) are then meta-analysed to address the study objectives. This design concentrates data collection in the two months before and the two months after implementation at a hospital; this is more efficient than a parallel-group cluster randomised design with four months of data collection at each cluster [9]. Figure 2 demonstrates an example timeline for site participation.

METHODS

Participants, interventions and outcomes

Study setting

Any hospital or surgical unit that routinely performs elective and/or emergency colorectal surgery may be included without restriction by country, unit size or case volume. Sites must identify a surgical, trainee, anaesthetic and nursing principal investigator, and complete local governance approvals to be eligible for randomisation in the study.

Eligibility criteria

All, consecutive, adult patients (age 18 years and above) undergoing right colectomy or ileocaecal resection with or without primary anastomosis can be included, including those who do not have an anastomosis or are defunctioned by a proximal stoma.

Inclusion criteria

- Adults ≥18 years of age.
- Right colectomy, defined as any colonic transection with the distal resection margin proximal to the splenic flexure.

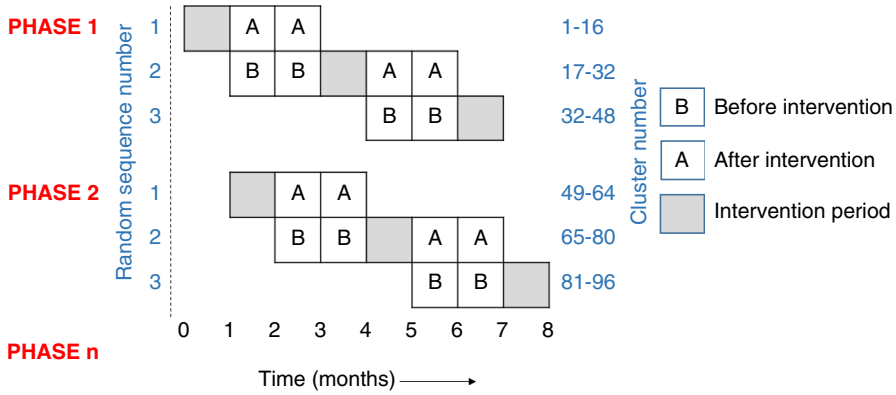

FIGURE 1 Dog-leg study design: The figure shows two dog-leg phases each with three randomisation sequences. In the first, 48 hospitals (clusters) are ready to recruit and these are randomised between three sequences. All three sequences are eventually exposed to the intervention. Sequence 1 immediately 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 dog-leg 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, seven dog-leg phases with 48 hospitals (336 hospitals total) each will achieve the sample size required (333 clusters)

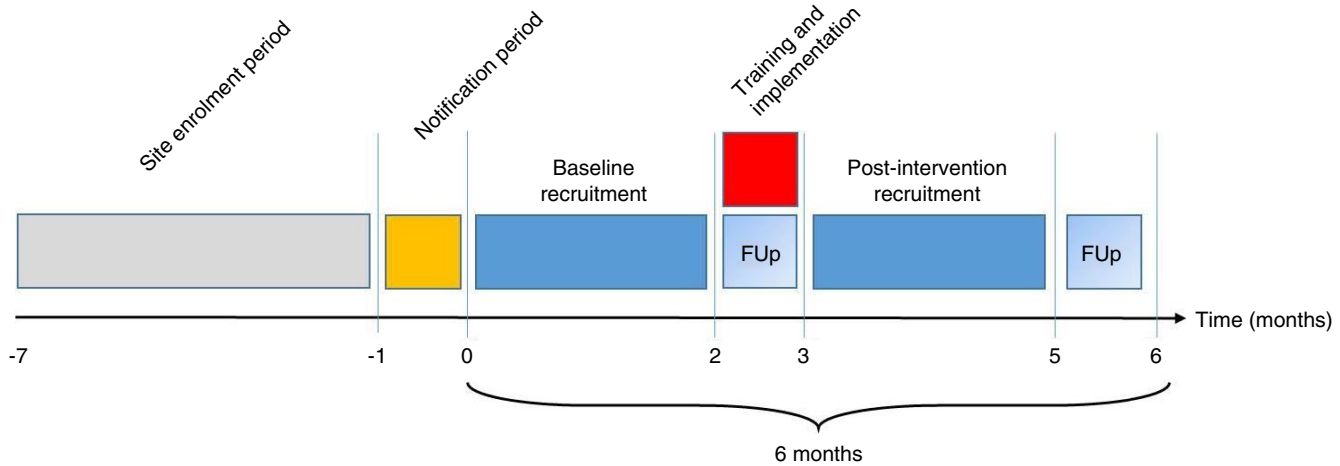

FIGURE 2 Example timeline for site and patient participation for randomisation to sequence 2

- Procedures for any pathology (benign or malignant), via any operative approach (open, laparoscopic, robotic or converted).
- Patients undergoing elective (during a planned admission), expedited or emergency surgery (during an unplanned admission).
- Patients undergoing colectomy and a synchronous procedure on a different organ e.g. hepatic metastatectomy.

Exclusion criteria

- Patients undergoing more than one gastrointestinal anastomosis during the index operation.
- In Crohn's disease, additional upstream strictureplasty or resection/anastomosis to treat disease or strictures at the same operation.
- Patients undergoing concurrent hyperthermic intra-peritoneal chemotherapy (HIPEC) and/or cytoreductive surgery.
- Individual patients should only be included in EAGLE once. Following the index EAGLE study procedure, patients undergoing further operative treatment within the study window should not have repeated entries created.

Co-enrolment

The EAGLE study permits co-enrolment into other research studies provided the study intervention does not evaluate technical or perioperative interventions where anastomotic leak is the primary outcome measure.

Consent

Patients will undergo consent for their operation as per routine care. Patient-level consent for research is not necessary in many countries (for example, Health Research Authority guidance in the UK), as the intervention entails hospital-level education. Patient-level informed consent for research will be obtained by the surgeon or research nurse in countries where consent is a requirement (Appendix S1) {32}.

Interventions

Background

We performed a systematic review of published literature to provide evidence for the QII. Guidelines, meta-analyses, randomised studies and cohort studies addressing: (1) anastomotic risk stratification; (2) effectiveness of training for standardisation of anastomotic practice; (3) intra-operative checklists related to formation of anastomosis, were included (date of last search: 01 May 2019). From 492 initial search results, 16 pre- or intra-operative risk scores for prediction of anastomotic leak following colorectal resection were identified. Nine studies reported score performance following internal validation, with area under the receiver operating characteristics curve (AUROC) ranging from 0.62 to 0.92. Only four risk scores were externally validated in independent datasets, with an AUROC ranging from 0.58 to 0.96; the best performing risk score was the anastomoticleak.com calculator [10,11]. No multi-centre studies looking at the effectiveness of training of a standardised anastomotic technique, or intra-operative checklist relating to the formation of a colorectal anastomosis were identified.

EAGLE Safe Anastomosis Quality Improvement Intervention (QII)

The EAGLE study intervention phase involves the completion of online education modules by collaborating surgeons, and site-level implementation (e.g., department presentations and discussion) for surgeons, anaesthetists and operating room staff. The three-part behavioural change QII is taught across five e-modules and composed of:

Patient-level preoperative risk stratification for anastomotic leak. Preoperative risk should be calculated for each patient undergoing right colectomy or ileocaecal resection using the anastomoticleak.com risk calculator [10]. Investigators will be encouraged to preoperatively calculate the leak risk with or without an intra-operative complication. This dynamic risk estimate can be used to inform shared decision making with the patient both preoperatively and in light of any intra-operative events as part of the ECSP Safe Anastomosis Checklist.

ESCP Safe Anastomosis Checklist. The ESCP Safe Anastomosis Checklist should be implemented in theatre, immediately prior to formation of an anastomosis or a stoma, and either before or after transection of the bowel at the surgeon's discretion. 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 consists of three main questions (Appendix S2):

1. Are there any concerns from the anaesthetist or theatre team?
2. Does the surgical team feel it is appropriate to proceed to anastomosis? Are there any unforeseen intra-operative complications that could increase baseline risk calculation?
3. If yes to anastomosis, what type of anastomosis is planned?

As per the WHO Surgical Safety Checklist [12], local adjustment of the checklist at participating centres is permitted. A paper copy of the Safe Anastomosis Checklist should be stored inside the clinical notes.

Harmonised technique for stapled and hand-sewn anastomosis. This module presents the best available evidence for both stapled and hand-sewn anastomoses to inform anastomotic decision making. The evidence presented in the education modules is taken from a systematic review and a two-stage modified Delphi exercise that was undertaken by over 200 specialist colorectal surgeons from

around Europe [13]. This consensus process has enabled guidance to harmonise practice where high-quality evidence was not available.

Intervention timing

The QII will be delivered at each site (cluster) at a specific time point determined by randomisation sequence. Local research teams will only receive passwords to access QII materials during the intervention phase to ensure they are not exposed to the study intervention in "control" periods. Pre-intervention data will act as 'control' data for the QII comparator.

Training platform

The EAGLE Anastomotic Leak Prevention training platform is accessible at https://eagle-escp.eu.com. Login details will be sent to all general and colorectal surgeon consultants and trainees at participating sites, identified by the site PIs. All surgeons will be encouraged to complete the modules during the four week intervention period.

Criteria for clusters to discontinue their participation in the study, strategies to improve adherence and relevant concomitant care are outlined in the supplementary material Appendix S1.

Outcomes

Primary outcome

The primary outcome measure is anastomotic leak within 30 days of surgery (with day of surgery as day 0). Anastomotic leak is defined according to the ESCP consensus definition as a leak or intra-peritoneal (abdominal or pelvic) fluid collection identified radiologically or clinically [2]. The rate of leak will be defined as a proportion of patients who had a primary anastomosis (rather than total patients undergoing right hemicolectomy or ileocaecal resection).

Secondary clinical outcomes (all limited to 30 days)

- Rate of clinical leak, that is, Grades B and C, (Grade A – no further procedural intervention, radiologically diagnosed; Grade B – radiological reintervention; Grade C – surgical reintervention which may include laparoscopy or laparotomy). See Appendix S1 for further details about anastomotic leak grading in this study.
- Rate of reoperation for anastomotic leak
- Rate of adverse outcomes (total operated patients as denominator), specifically:
  a. Reoperation for any cause
  b. Unplanned admission to critical care
  c. Readmission to hospital
  d. Postoperative mortality
- Length of hospital stay
- Rate of stoma formation at index operation, either
  a. Stoma without primary anastomosis, or
  b. Defunctioning ileostomy with primary anastomosis

Secondary process outcomes

A process evaluation will be undertaken to report rates of site enrolment, time taken to gain approvals and site attrition; cluster (hospital) and patient-level recruitment; rates of completion of the QII online training modules and adherence to their components; and reported barriers and enablers of practice change at cluster level. Further details may be found in the Appendix S1.

Participant timeline

Clusters (hospital teams) will register for the study and once local approvals have been granted, will be randomised to one of three sequences of data collection and implementation of the intervention (Figure 3).

Sample size and recruitment

The EAGLE study is designed to detect an absolute reduction in anastomotic leak rate from 8.1% to 5.6% (relative risk reduction

Randomisation sequence	Week 1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32
Sequence 1	Intervention	Data collection (After only)	Data collection (After only)	30 day follow-up	Complete	Complete	Complete	Complete
Sequence 2	Standby	Data collection (Before)	Data collection (Before)	Intervention (and 30 day follow-up)	Data collection (After)	Data collection (After)	30 day follow-up	Complete
Sequence 3	Standby	Standby	Standby	Standby	Data collection (Before only)	Data collection (Before only)	Intervention (and 30 day follow-up)	Complete

FIGURE 3 EAGLE Phased Cluster Randomisation schedule of activity

30%). ESCP audit data (2015) suggest an intra-class correlation coefficient (ICC) of approximately 0.05 and a mean recruitment rate of 10 patients per 8-week recruitment period (Table 1) [2]. An overall "design effect" or sample size inflation factor for our cluster-randomised dog-leg design relative to an individually-randomised parallel-groups design was calculated [14]. Using this design effect, to detect a reduction in leak rate from 8.1% to 5.6% with 80% power at the 5% significance level requires 292 clusters and 3895 patients. In practice there will be variation in patient recruitment at different hospitals, which can be expected to increase the required sample size. Following a published rule of thumb [15], we assume that this inflates the sample size by at most 14% leading to a required sample size of 333 clusters and 4440 patients.

Cluster randomisation and blinding

Cluster randomisation

Randomisation of hospitals will be conducted in sequential phases. Within a phase, hospitals (clusters) with completed local approvals will be organised into matched triplets according World Bank country income classification (low, lower middle, upper middle or high income), whether the hospital accepts referrals from other hospitals for patients needing right colectomy (referral hospital or non-referral hospital) and according to cluster size (total number of hospital beds). Triplet matching will be completed manually by the project manager and sequence allocation will be generated by a REDCap randomisation module [16], (three possible randomised sequences) as demonstrated in Figure 1.

Blinding

Patients will be unaware of whether the ESCP Safe Anastomosis Intervention has been implemented at their hospital at the time of their surgery. Surgeons and outcome assessors will not be blinded to intervention status. Assessors will be required to collect data for the objective primary endpoint (anastomotic leak) in a standardised manner. The senior trial statistician will be blinded to allocation sequence until the database for that phase of the trial has been locked.

TABLE 1 Patient recruitment rates in two months from 2015 ESCP right colectomy audit [2]

Number of patients	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)

Data collection and management

Patient identification

Each participating cluster will create local systems to identify all eligible patients. Ideally patients will be identified pre-operatively, but they may be identified at any of the following opportunities:

- Preoperative: surgical outpatient clinics (i.e., at the time of planning elective surgery); planned theatre lists (i.e., at the time of admission for surgery); emergency surgical admissions (i.e., at the time a decision is made to operate)
- Intra-operative: by the operating team during the in-theatre Safe Anastomosis Checklist, once procedure eligibility has been confirmed
- Postoperative but before discharge: by either the operating surgeon or upon review by the research team

Patients can be identified by a doctor involved in the patient's care or a research nurse.

Data collection

Local Principal Investigators will establish pathways in their hospitals to ensure accurate data collection. Intra-operative checklists will be stored in patient notes. Source data will be held in the patient's medical record (electronic or paper) and extracted to either a paper case report form (CRF) (Appendix S3), or directly to the REDCap database [16]. All patients undergoing right colectomy, (including those who do not have a primary anastomosis) will be prospectively enrolled in the study and will be followed-up to 30 days postoperatively (with day 0 being the day of surgery).

Data management

When data are uploaded onto the EAGLE REDCap database, each patient will be allocated a unique REDCap identifier and local investigators must keep a secure list of EAGLE patients with their REDCap identifiers. The unique study numbers will be used in any correspondence between the EAGLE study office and the site.

Completing follow-up

The EAGLE study will only use routinely collected data. Patients will not undergo any additional investigations for the study and clinical follow-up will be limited to review of health records up to 30 postoperative days.

Post-study care

There is no additional patient contact (telephone or in-person) planned beyond what is normal clinical practice at each centre.

Confidentiality

Only anonymised patient data will be uploaded to and stored in the REDCap database. 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. Further details about data security may be found in the Appendix S1.

Statistical methods

Methods for analysis

Primary objective and outcome

In the primary analysis of each phase, 30-day leak rate will be modelled using mixed effects logistic regression with random cluster (hospital) effects to estimate the effect of intervention (A vs. B in Figure 1) adjusting for time period (first period of data collection is from week 5 to week 12; second period of data collection is from week 17 to week 24). The analysis will also adjust for patient's gender, operative urgency and the characteristics used to match hospitals in the randomisation (insofar as these vary within the phase): hospital size (<500 vs. ≥500 beds); country income classification (high vs. middle or low); and whether the hospital accepts referrals from other hospitals for patients needing right colectomy. Randomised trials routinely adjust for prognostic factors at baseline – including those used to stratify or match the randomisations – even though these are expected to be balanced by randomisation, because adjustment increases precision and statistical power [17,18]. In the present case we are limiting the overall number of covariate adjustments to avoid over-fitting the regression model in each phase. The log odds ratio for the intervention effect (with its standard error) will be extracted from the mixed logistic regression analysis for each phase, and pooled in a random effects meta-analysis using the inverse variance approach of DerSimonian and Laird [19]. A forest plot will also be presented, and a 95% confidence interval and 95% prediction interval for the intervention effect will be calculated.

Secondary outcomes

Secondary outcomes will be analysed with mixed effects logistic regression exactly as for the primary outcome. Most secondary outcomes are dichotomous (occurrence of clinical leak, reoperation for anastomotic leak; reoperation for any cause; unplanned admission to critical care; readmission to hospital; postoperative mortality; stoma without primary anastomosis; defunctioning ileostomy with primary anastomosis). Length of hospital stay will be dichotomised for the purpose of analysis into ≤10 days or >10 days.

Exploratory subgroup analyses

Pre-planned subgroup analyses will be conducted to see whether any of the following factors modify the effect of the intervention; because of the number of factors the results will be considered exploratory and interpreted with caution.

At cluster (hospital) level:

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

At patient level:

- Indication for surgery (malignant vs. benign)
- Procedure urgency (elective vs. expedited/ emergency)
- American Society of Anaesthesiologists (ASA) grade
- Operative approach (open vs. laparoscopic/ robotic)
- Anastomotic technique (stapled vs. hand-sewn anastomosis)
- Primary operating surgeon grade as reported (trainee vs. consultant)
- Primary operating surgeon specialism as reported (general vs. colorectal surgeon)

For each of the factors above an interaction will be investigated by fitting a mixed logistic regression model for each phase, as for the primary analysis, but with the addition of a main effect of the factor (if not already included in the primary analysis model) and an interaction between intervention and the factor in the logistic model. The log of the ratio of odds ratios representing the interaction (with its standard error) will be extracted from this mixed logistic regression analysis for each phase, and pooled in a random effects meta-analysis, as for the primary analysis.

Interim analyses

No formal interim analyses are planned.

Missing data

The primary analysis will be by intention to treat. Estimating an intention-to-treat effect does not require outcomes to be available for every patient, but it does assume every effort has been made to collect complete outcome data [20]. Our primary, mixed logistic regression analysis in each phase will include all patients with

non-missing outcome. This approach is valid and unbiased under the assumption that missingness in the outcome is systematically related only to the covariates and other variables that are included in the analysis model (a "missing at random" assumption) [20,21]. For the primary outcome of anastomotic leak, secondary analyses will explore the sensitivity of the conclusion from the primary analysis to plausible departures from the missing at random assumption, for example using multiple imputation or pattern mixture modelling [20].

Oversight

Oversight and monitoring committees are described in detail together with data sharing plans, safety considerations, insurances and auditing in the supplementary material (Appendix S1).

Ethics approval and consent to participate

The study will be carried out in accordance with ethical principles as mandated by each participating country. In the UK, this is in accord with Research Governance Framework for Health and Social Care, Second Edition, 2005 and the study has been approved as research without patient level consent by the Health Research Authority; IRAS project ID 272250; protocol number RG_19-196; REC reference 19/HRA/5656. The University of Birmingham will act as sponsor to all sites on signing the study agreement in collaborating sites/countries.

The intervention is low-risk with no specific hazards anticipated. As a pragmatic study, the educational e-modules are intended to inform clinical practice and harmonise care but we recognise that clinical teams will exercise their own clinical judgement and determine appropriate care for each individual patient. Patients will receive usual pre- and postoperative care unaffected by the intervention.

We anticipate that most ethics review boards will waive any 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 principal investigators in each participating country to seek local research ethics committee advice to determine whether informed consent should be sought.

DISCUSSION

EAGLE is an ambitious wide-reaching global study that aims to reduce the rate of the most serious colorectal complication and to save lives. Regardless of the impact on the primary outcome measure, it will disseminate best evidence and promote conversation around anastomosis in surgical units around the world. The novel study design and rapid timeline will also prove the design concept for future QII studies.

EAGLE has been designed pragmatically to be delivered quickly, across diverse settings within a short study timeline. Study procedures have been optimised to minimise burden to investigators, so that it can be delivered without the requirement for research nurse or financial support. Patient level consent will not be required across most countries, facilitating consecutive and complete recruitment. Shared decision-making will be encouraged which fits with a wider-reaching move in surgery for patient-centred and individually tailored care. Due to the study including all patients undergoing a right colonic resection, any change in the anastomotic leak rate will not be masked by an overall change in the proportion of patients undergoing primary anastomosis.

Whether or not EAGLE achieves clinically significant reduction in complications, it is designed to deliver best evidence to consultant and training surgeons to be used in conjunction with their anaesthetic and wider theatre teams. Beyond its potential to improve patient care and save lives EAGLE has the potential to promote conversation, teamwork and morale.

Limitations

Secondary effects of the EAGLE study cannot be fully predicted; it is possible that the study will result in increased stoma formation which may be considered an unwelcome consequence by some patients (and theoretically for some might have been unnecessary). It is recognised that limiting follow-up to 30 days will miss a very small minority of leaks occurring after this time (vast majority occur <14 days).

To anticipate a 30% risk reduction in anastomotic leak by way of a quality improvement intervention delivered through educational materials assumes first the education material will be used by a significant body of surgeons in participating centres, and second that there will be some behaviour modification. This may occur either by direct application of the QII materials and/or by inviting thought and consideration around anastomotic practice. Literature supports the need for fidelity to QIIs in order to observe improvements in safety [22] and evidence to show that these types of interventions rely on encouraging thinking about care rather than particular changes being made.

Covid-19 adaptation

Five weeks after its launch, with 32 sites active and a further 23 already randomised to a sequence, EAGLE was temporarily suspended in March 2020, partly relaunching in July 2020 and fully in October 2020. Although this has affected to some extent the design of the first phases, EAGLE's novel multi-phased study design has serendipitously enabled the flexibility of timetabling required to mitigate interruptions of this kind.

SUMMARY

EAGLE is an international, multi-centre, cluster randomised-sequence quality improvement study, which provides the opportunity for the

general and colorectal surgical communities to come together to improve care in colorectal surgery. It will ignite discussion with peers and patients about anastomotic decision making and help to understand whether this novel way of evaluating a quality improvement process is feasible and translates into measurable clinical benefit for patients.

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CONFLICT OF INTERESTS

MF acts as a consultant for Johnson & Johnson Medical N.V. The other authors declare no conflicts of interest and study sites are not paid for their contributions to the study.

ETHICS APPROVAL

Health Research Authority (HRA) approval has been obtained for the EAGLE study as research *without* patient level consent; REC reference 19/HRA/5656 (see Appendix S5; HRA approval pdf attached).

PATIENT CONSENT STATEMENT

Patient-level consent for research is not necessary in many countries (for example, Health Research Authority guidance in the UK), as the intervention entails hospital-level education. Patient-level informed consent for research will be obtained by the surgeon or research nurse in countries where consent is a requirement (Appendix S1) {32}.

AUTHOR CONTRIBUTIONS

Conception and design: protocol writing group, study management group and operations committee. Intervention design: protocol writing group and education committee. Manuscript writing, final approval of manuscript and accountability: all authors.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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