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Randomized Clinical Trial

Evaluation of a quality improvement intervention to reduce anastomotic leak following right colectomy (EAGLE): pragmatic, batched stepped-wedge, cluster-randomized trial in 64 countries

ESCP EAGLE Safe Anastomosis Collaborative and NIHR Global Health Research Unit in Surgery

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Abstract

Background: Anastomotic leak affects 8 per cent of patients after right colectomy with a 10-fold increased risk of postoperative death. The EAGLE study aimed to develop and test whether an international, standardized quality improvement intervention could reduce anastomotic leaks.

Methods: The internationally intended protocol, iteratively co-developed by a multistage Delphi process, comprised an online educational module introducing risk stratification, an intraoperative checklist, and harmonized surgical techniques. Clusters (hospital teams) were randomized to one of three arms with varied sequences of intervention/data collection by a derived stepped-wedge batch design (at least 18 hospital teams per batch). Patients were blinded to the study allocation. Low- and middle-income country enrolment was encouraged. The primary outcome (assessed by intention to treat) was anastomotic leak rate, and subgroup analyses by module completion (at least 80 per cent of surgeons, high engagement; less than 50 per cent, low engagement) were preplanned.

Results: A total 355 hospital teams registered, with 332 from 64 countries (39.2 per cent low and middle income) included in the final analysis. The online modules were completed by half of the surgeons (2143 of 4411). The primary analysis included 3039 of the 3268 patients recruited (206 patients had no anastomosis and 23 were lost to follow-up), with anastomotic leaks arising before and after the intervention in 10.1 and 9.6 per cent respectively (adjusted OR 0.87, 95 per cent c.i. 0.59 to 1.30; $P = 0.498$). The proportion of surgeons completing the educational modules was an influence: the leak rate decreased from 12.2 per cent (61 of 500) before intervention to 5.1 per cent (24 of 473) after intervention in high-engagement centres (adjusted OR 0.36, 0.20 to 0.64; $P < 0.001$), but this was not observed in low-engagement hospitals (8.3 per cent (59 of 714) and 13.8 per cent (61 of 443) respectively; adjusted OR 2.09, 1.31 to 3.31).

Conclusion: Completion of globally available digital training by engaged teams can alter anastomotic leak rates. Registration number: NCT04270721 (http://www.clinicaltrials.gov).

Research in context

This study focused on reducing a serious complication called anastomotic leak (occurring in 8 per cent of patients) after right colectomy, a common bowel operation. The authors developed a global programme called EAGLE, involving 64 countries and 3268 patients. The programme included online training for surgical techniques, a digital risk calculator, and an in-theatre checklist. Although the overall leak rates did not decrease, hospitals with over 80 per cent team engagement saw reduced leak rates. This study highlights the importance of team involvement in implementing interventions successfully. The EAGLE programme is a cost-effective and scalable solution for preventing anastomotic leaks. Surgeons, including trainees, can access the training module at https://eagle-escp.eu.com/.

Introduction

Right colectomy is performed most frequently for cancer (78 per cent)[1] or Crohn's disease (12 per cent)[2], by both general and specialist surgeons in high- and lower–middle-income countries. Anastomotic leak arises in over 8 per cent of patients with a 10-fold increased risk of postoperative death[3]. When it occurs, there is frequently the need for a stoma, a two-fold increased risk of cancer recurrence[4], and reduced cancer-specific survival after cancer surgery. A James Lind Alliance Priority Setting Partnership[5] identified anastomotic leak as a research priority for patients as there has been little improvement recently[4,6].

A multinational audit[2,3] demonstrated variation in surgical techniques and anastomotic leak rates. It also identified patient and disease factors to be additional major risk indicators for

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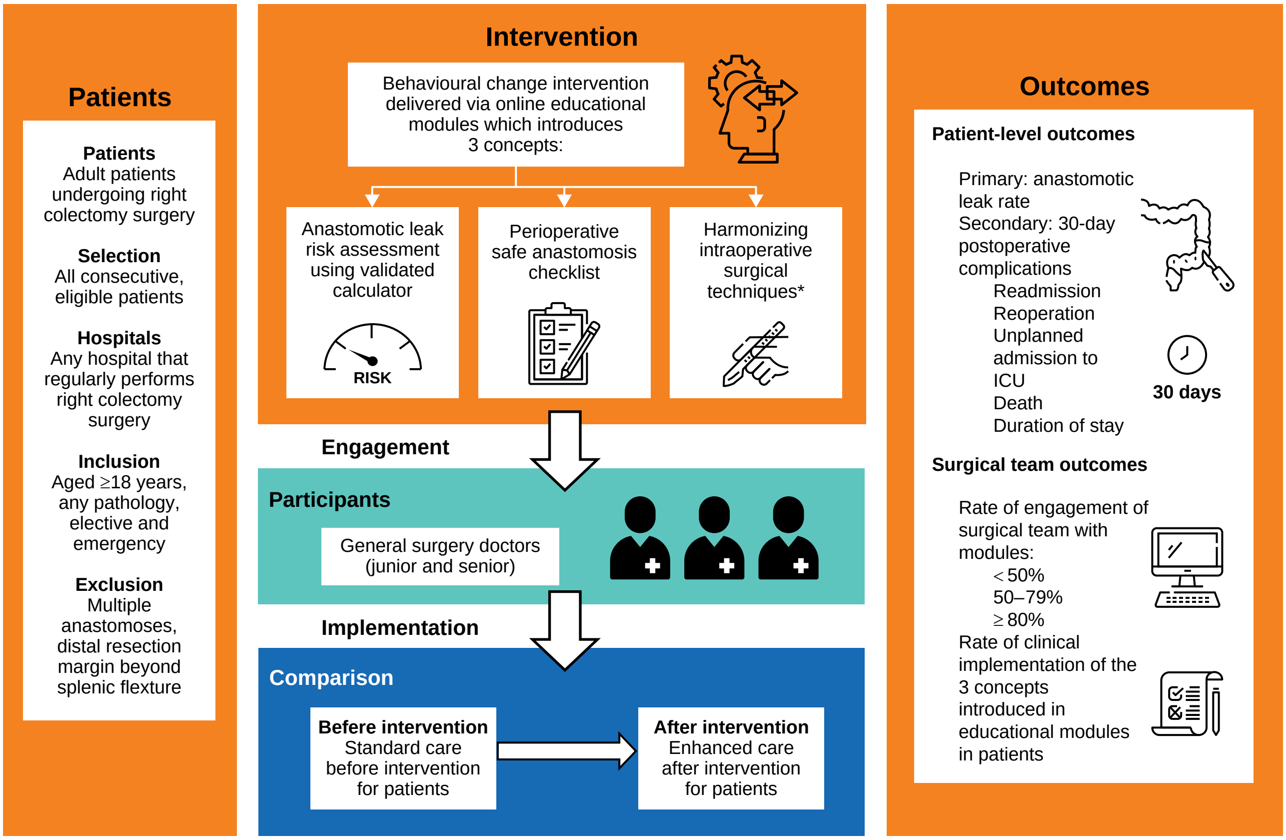

Fig. 1 Modified PICO graph for EAGLE study

*Harmonizing of intraoperative techniques is a suite of learning materials, discussions, and operative videos that explore the challenges that may face surgeons during operation and supports surgeons' decision-making by presenting the best evidence available on how to tackle these challenges. PICO, patients, intervention, comparator, outcome.

anastomotic leaks[1]. These multiple factors point to numerous stages of success or failure, and indicate that the application of a complex intervention based on the Medical Research council/ National Institute for Health Research (NIHR) framework appear to provide the most appropriate approach. The aim of EAGLE was to develop a quality improvement intervention that included behavioural change tested by prospective, randomized methodology[7].

Methods

Intervention development

The quality improvement intervention was developed based on the Medical Research Council framework for complex interventions[8] and the COM-B (Capacity, Opportunity, Motivation, Behaviour) model[9,10] for behavioural change (*Fig. S1*). The authors acknowledged that quality improvement and behavioural change can be time-consuming, so EAGLE was designed to be pragmatic, prioritizing engagement. EAGLE was investigator-initiated and investigator-led.

The intervention was co-developed through iterative cycles with key stakeholders, including a diverse global team of senior surgeons, anaesthetists and theatre staff, surgical trainees, patient representatives, methodologists, and statisticians. In 2018, a Delphi consultation was conducted with 200 senior surgeons from 30 countries to underpin the content domains of the programme. Online learning was selected as the main strategy for delivering training (*Appendix S1*) because it offered the opportunity for learners from different parts of the world to engage with educational packages despite separation in geography, time zones, and chronological time (across the batched study). A scoping review was undertaken to identify a validated, high-quality, easy-to-use anastomotic leak risk calculator. The quality improvement programme was further refined by a core team of multinational consultant and trainee surgeons, and patient representatives for online learning and in-theatre checklists (*Appendix S2*). Pilot modules were developed and presented in May 2019 to 200 surgeons, and a consultation exercise was conducted for feedback, suggestions, and identifying and troubleshooting problems. Online modules were further refined and beta-tested by 50 surgeons, leading to a final round of changes in July 2019.

Intervention description

EAGLE was a complex intervention, providing a hospital-level educational programme targeted at surgical teams. Patients who underwent surgery before the intervention received standard care, and those who had surgery after the intervention received treatment by surgical teams that were exposed to the EAGLE Safe Anastomosis programme. The intervention was an online educational platform, delivered at the hospital level and implemented at patient level. It comprised three components (*Fig. 1*). The first was an anastomotic leak risk calculator (anastomoticleak.com[11,12]), which is an online validated tool for calculating the risk of anastomotic leak (with additional intraoperative recalculation, if necessary). A risk calculation tool was chosen provided an objective, evidence-based estimation of leak risk. Use of the tool before operation allowed the hospital

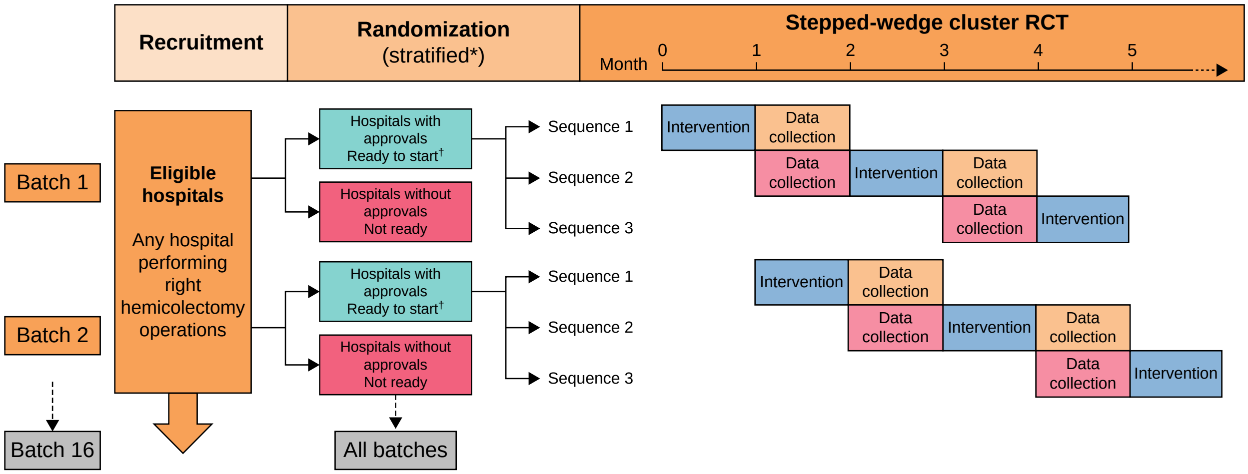

Fig. 2 Trial design schematic

*Randomization stratified by number of beds, referral or non-referral hospital, country income. †Minimum of 18 hospitals per batch to be ready for randomization.

team time to assess risks and plan the optimal procedure with each patient. Importantly, it facilitated shared decision-making with the patient by opening dialogue and quantifying their individual leak risk. The specific risk tool was chosen as it was the only one available that had been externally validated[11,12]. The second component, the EAGLE Safe Anastomosis Checklist, is an intraoperative checklist involving the whole theatre team, used immediately before forming an anastomosis (*Appendix S3*). This checklist instituted a pause in theatre activities immediately before the decision was made to form an anastomosis, and/or regarding the configuration and technique of stoma formation. This offered an opportunity for the whole team to reassess the operation and the stability of the patient, and voice any concerns to facilitate team decision-making. The final component was a harmonization of surgical techniques package, aimed at unifying the wide variety of operative approaches previously observed in the European Society of Coloproctology (ESCP) audits. The online educational package curriculum is summarized in *Appendix S2* and can be accessed at https://eagle-escp.eu.com/.

Engagement and completion

The authors set out to maximize completion, defined as the number of surgeons who finished all five modules of the online learning materials, and team engagement, defined as the proportion of surgeons who completed all five modules in each hospital team. Access to the modules was provided at the start of a 4-week intervention interval, within hospital teams in each sequence (*Fig. 2*). The principal investigators (PIs) (surgeon, anaesthetist, and lead theatre staff member) from each hospital were invited to a webinar, in which they were introduced to the module structure and content. They were also provided with a slide set that was editable to create bespoke presentations tailored to their teams. Three separate slide sets were produced for surgeons, anaesthetists, and theatre staff.

The surgical PI provided and registered the contact details for all members of their team, who they felt could participate in the study. This was to maximize engagement, but it was recognized that individual surgeons within a cluster could, and would, choose not to undertake the online modules. This design enabled the impact of team engagement to be assessed within the trial structure. An individual login was provided to each registered surgeon for the online modules.

A webinar was hosted for each batch of clusters before they opened to recruitment. This included hospital teams that had and had not received the intervention, and so made no reference to the online modules. A separate webinar for each batch of clusters was hosted before the intervention was undertaken. Update webinars were held for all investigators every 3 months to share progress in trial development and delivery; a link to an example of a webinar can be found in *Appendix S3*.

Trial design, ethics, and approvals

EAGLE was an international, multicentre, batched, cluster-randomized study, in which clusters were individual hospital teams (*Fig. 2*). As the study involved implementation of team training, a cluster-randomized design, with each hospital team as a cluster, was necessary. A stepped-wedge design was chosen instead of a conventional parallel-arm cluster trial to maximize statistical efficiency, so that all clusters would eventually be exposed to the intervention and could act as their own control[13,14]. This also facilitated timely, equitable access to the evidence-based educational materials by all teams, irrespective of which arm they were randomized to. A batched design was adopted so that randomization could occur in batches, depending on the readiness of individual hospital teams and obtaining local approvals[15,16]. This made the trial pragmatic as hospital teams did not all need to start the intervention at the same time. It also minimized the time from randomization to intervention, and minimized any potential bias or contamination. Recognizing that the intervention could not be withdrawn from a hospital once it had been implemented, an incomplete stepped-wedge (specifically, a dog-leg) design was finally chosen[17,18]. The hospital teams were randomized in batches once a suitable number were ready (*Fig. 2*). A minimum of 18 hospital teams were randomized in each batch and stratified to minimize any potential bias in differing hospital characteristics in each randomization arm (*Fig. 2*). Hospital teams in each batch were randomized in a dog-leg design to three possible sequences with up to two intervals of data collection. In the first sequence, the intervention was implemented before any data collection took place, and data were collected in the first interval only. In the second sequence, data were collected in both intervals, with the intervention implemented in between. In the third sequence, the intervention was not implemented until after data collection, and data were collected in the second interval only. This incomplete stepped-wedge design was chosen to maximize statistical efficiency and minimize the burden of data collection. More detail on the design and lessons learned from its implementation have been reported previously[15].

The study was registered at ClinicalTrials.gov (NCT04270721) and the protocol has been published[17]. As the intervention comprised training delivered at a hospital-level, Health Research Authority (HRA) approval was obtained for research not requiring patient-level consent in the UK (REC reference:19/HRA/5656). This was also the case for the large majority of hospitals, internationally. Where ethical approval was required, the national PI was responsible for obtaining this before the hospital was ready for entry into randomization. Consent was obtained for surgery as part of routine care and consent to research was not required in most countries, as the intervention was implemented at hospital level and the primary outcome derived from routinely collected patient outcomes.

Hospital eligibility, team structure

EAGLE was designed to be globally inclusive, enrolling any surgical unit that performed right colectomy regardless of hospital size or annual case volume (*Table S1*). Registration required identification of surgical, anaesthetic, and nursing PIs.

Patients and data collection

Consecutive patients, aged 18 years and over, undergoing right colectomy (including ileocaecal resection) for any indication or urgency were included in the study, whether or not an anastomosis and/or stoma was formed. Excluded were patients undergoing more than one anastomosis, those having additional synchronous procedures, and those undergoing a second eligible operation in the data collection window. The full inclusion and exclusion criteria are listed in *Appendix S3*. Routine patient data were collected from hospital notes and reported electronically via the Research Electronic Data Capture web application (REDCap; Vanderbilt University, Nashville, TN, USA)[19,20], hosted in the University of Birmingham, UK.

Outcomes

The primary outcome was anastomotic leak in patients who had a primary anastomosis, within 30 days of surgery (operation day was day 0). The study used the ESCP consensus definition of ‘leak or intraperitoneal (abdominal or pelvic) fluid collection identified radiologically or clinically’[6]. Follow-up was for 30 days after surgery. Routinely collected patient data were retrieved from medical notes, electronic health records or routine in-person assessments by the local team.

Secondary clinical outcomes were assessed at 30 days after operation, and included clinical leaks, reoperation for anastomotic leak, readmission to hospital, reoperation for any reason, unplanned admission to critical care, duration of hospital stay (10 or fewer *versus* more than 10 days), stoma formation (stoma without primary anastomosis and defunctioning ileostomy), and death.

Sample size and adjustments

The original sample size was calculated based on published evidence from ESCP audit data (2015)[6], with mean recruitment of 10 patients per 8-week recruitment phase, and an intraclass correlation coefficient of approximately 0.05; full details are available in the protocol[17]. Detection of a 30 per cent reduction in anastomotic leak from 8.1 to 5.6 per cent, was calculated to require 333 hospital teams and 4440 patients. *A priori* trial planning allowed sample size adjustments after the first look. Interim, blinded results from the first eight completed batches were presented to the Data Monitoring Committee, and subsequently to the Trial Steering Committee, showing that the leak rate aggregated across intervention and control arms was 9.0 per cent. For this aggregated leak rate of 9.0 per cent, the predicted difference in leak rate wound need to fall from 10.6 per cent in the control to 7.4 per cent in the intervention arm to represent a 30 per cent reduction in leak. The number of procedures observed in each data collection phase in each hospital averaged around 8, which was smaller than the figure of 10 assumed in the original sample size calculation. Following the *a priori* plan, sample size reassessment based on these figures produced a new minimum target sample size of 312 clusters and 3328 participants. Owing to the lower than anticipated patient recruitment per site, the Trial Steering Committee recommended that the original cluster target of 333 hospital teams should stand.

Randomization

When a batch of clusters was ready for randomization, the central team matched hospital teams into triplets that were matched according to: World Bank country income classification (low, lower middle, upper middle or high income; see *Appendix S3* for definitions)[21]; tertiary referral status (whether their hospital accepts referrals from other hospitals); and hospital size (total number of hospital beds, dichotomized to below 500 and 500 or more). The clusters in each triplet were then randomized to each of the three sequences. Cluster allocation was undertaken by the trial statistician using a REDCap randomization module (*Fig. 2*).

Blinding

Hospital teams did not receive the EAGLE intervention material until the start of their intervention interval, to prevent contamination. As a hospital-level intervention, neither surgeons nor hospital teams were blinded; however, patients were unaware of their hospital participation status. Study teams were required to collect outcome data objectively. They were unblinded to hospital intervention status.

Case ascertainment

To ensure consecutive case ascertainment, each hospital team nominated an independent assessor (usually theatre staff not part of the EAGLE hospital team) to identify retrospectively all eligible patients from theatre logbooks. These data were cross-checked by the Birmingham trials team. Inconsistencies resulted in rechecking the whole data collection period for that centre (*Fig. S2*).

Data validation

The EAGLE operations team completed missing data by direct contact with the local investigators. Data accuracy was also validated at two hospital teams per randomization sequence

(6 per batch; approximately 20 per cent of hospital teams), via a random number generator. A local nominated assessor completed the data validation on 10 key data points for up to the first 10 consecutive patients in a single data collection interval. Any hospital team with more than 10 per cent overall data inaccuracy was required to recheck the whole data collection.

Statistical analysis

Analysis followed the plan specified in the published protocol and the statistical analysis plan[17].

Primary outcome

In each study batch, the effect of the intervention on anastomotic leak rate was estimated using mixed-effects logistic regression with random cluster effects (normally distributed on the logistic scale) to estimate the effect of intervention adjusting for time interval, that is data collection interval 1 *versus* interval 2. Adjustment was also made for cluster matching characteristics (country income status, tertiary referral status, and hospital size) in so far as these varied within the batch, and for patient sex and operative urgency[22]. These co-variates were all categorical (for more details, see protocol in *supplementary material*). The log OR and standard error for the intervention effect were extracted from the mixed logistic regression analysis for each batch, and pooled in a random-effects meta-analysis using the inverse-variance approach of DerSimonian and Laird[23]. A forest plot was prepared showing the overall intervention effect, along with 95 per cent c.i. and *P* value.

Secondary outcomes

The plan was to analyse secondary outcomes in the same way as the primary outcome, but, owing to the low prevalence of secondary outcomes, frequent problems were encountered with convergence of the mixed regression model within individual batches. Therefore, in a change to the planned analysis, a single multilevel model was fitted to data from all batches, with batch as a random effect, and cluster within batch as a second level of clustering. This simpler analytical model fits a constant treatment effect across clusters rather than the random effect fitted by the meta-analysis of the primary outcome, but the authors wanted to fit as few random effects as possible to minimize the risk of non-convergence. The model adjusted for a fixed effect of the time period within the entire span of the study that data collection was conducted. This was assumed to be the same for all batches. The following prespecified secondary outcomes were assessed: occurrence of clinical leak; reoperation for anastomotic leak; reoperation for any reason; unplanned admission to critical care; readmission to hospital; postoperative death; stoma without primary anastomosis; and defunctioning ileostomy with primary anastomosis. For the purpose of analysis, hospital stay was dichotomized into 10 or fewer *versus* more than 10 days.

Subgroup analyses

To assess possible modification of the intervention effect, planned subgroup analyses were conducted for prespecified hospital- and patient-level characteristics. Hospital-level characteristics were: number of hospital beds (less than 500, or 500 or more); right colectomy volume (below 10, or 10 or more per 2-month interval); early *versus* late involvement in the trial (batch 1–8 or batch 9–16); health service expenditure; World Bank income group; proportion of operating surgeons who completed the online educational modules (less than 50, 50–79, or at least 80 per cent). Patent-level characteristics were: indication; urgency; ASA grade[24]; operative approach (laparoscopic, robotic or open); anastomosis formation technique (stapled or handsewn); primary operating surgeon grade; and primary operating surgeon specialism. The plan for each characteristic was to fit a mixed logistic regression model in each batch (as for the primary analysis), but with the addition of a statistical interaction between the potential effect modifier and the intervention effect. The log of the ratio of ORs representing the interaction (with its standard error) would be extracted for each batch and pooled in a random-effects meta-analysis, as for the primary analysis. In practice, model convergence issues arose, similar to those encountered with secondary outcomes, and, in a change to the planned analysis, a single multilevel model was fitted to all batches, as for the analyses of secondary outcomes. Owing to the number of factors considered in these subgroup analyses, the results were considered exploratory and to be interpreted with caution.

Sensitivity analysis

Planned sensitivity analysis was limited to per-protocol analysis of the primary outcome. Because of the unforeseen impact of the COVID-19 pandemic on the trial, an additional sensitivity analysis was undertaken that excluded the first two batches, which were interrupted.

Missing data

The mixed logistic regression analyses included only patients with complete outcome data. This approach is valid and unbiased under the assumption that missingness in the outcome is systematically related only to the co-variates and other variables that are included in the analysis model (a missing-at-random assumption). For inclusion in the primary intention-to-treat analysis, patients must have had a primary anastomosis formed and had surgery within the data collection time interval specified by the design. Recorded data collected outside of this interval (in error) were excluded.

Results

Between 3 February 2020 and 1 December 2022 (including a 5-month pause owing to the global SARS-CoV-2 pandemic lockdown), the EAGLE study randomized 355 hospital clusters, in 16 batches, from 64 countries (*Fig. 3*). For each randomization batch, the sequence allocation and exclusions are detailed in *Fig. S4a,b*. A total of 15 clusters (4.2 per cent) (hospital teams) withdrew from the study before patients were recruited and a further 8 (2.3 per cent) who did not enter any patients during the data collection interval, leaving 332 hospital clusters in the study. Some 141 hospital teams (39.2 per cent) were from low- and middle-income countries (*Table 1*). Both hospital stratification factors (*Table 1*) and patient variables (*Table S3*) were distributed evenly across the three randomization sequences. The need for emergency intervention varied between regions, as did patient characteristics: hypoproteinaemia was more common in Asia and Africa, and obesity and anticoagulation more common in Europe (*Table S1*).

From 332 hospital teams, a total of 3268 patients were included in the trial. Patient flow is shown in *Fig. 4*, and detailed by randomization batch in *Fig. S4a,b*. Some 217 patients (6.3 per cent) underwent stoma formation without anastomosis. Primary outcome data were missing for 23 of 3062 patients (0.7 per cent).

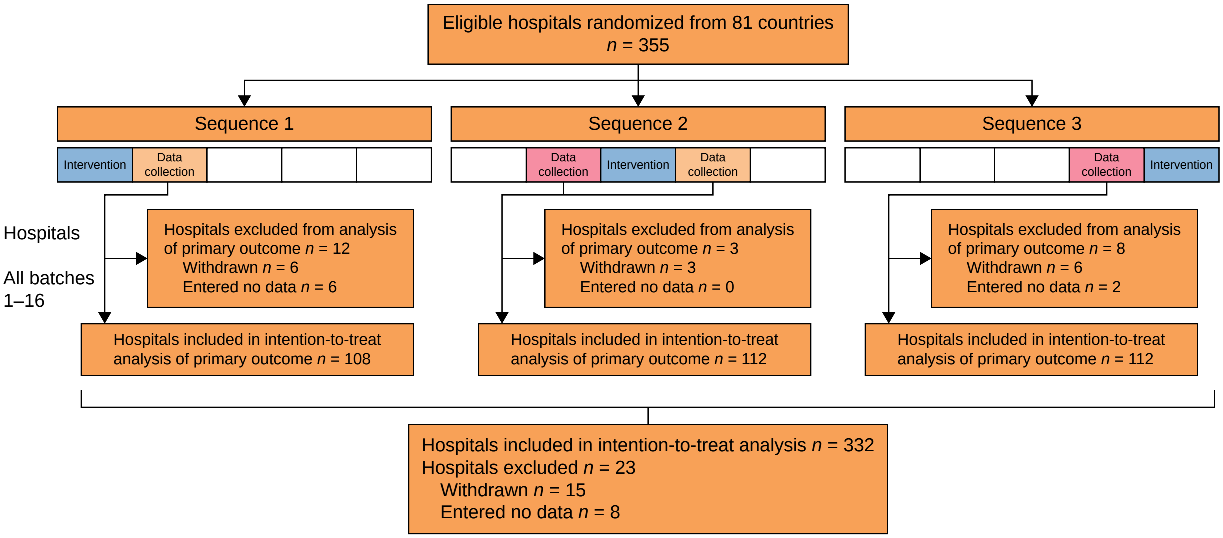

Fig. 3 **Hospital-level CONSORT diagram**

Table 1 Hospital characteristics by randomization sequence

	Sequence 1 $n = 120$	Sequence 2 $n = 115$	Sequence 3 $n = 120$
No. of beds			
< 500	53 (44.2)	49 (42.6)	56 (46.7)
≥ 500	67 (55.8)	66 (57.4)	64 (53.3)
Type of hospital			
Referral	96 (80.0)	91 (79.1)	90 (75.0)
Non-referral	24 (20.0)	24 (20.9)	30 (25.0)
Region			
Africa	8 (6.7)	12 (10.4)	7 (5.8)
Asia	23 (19.2)	20 (17.4)	18 (15.0)
Europe	76 (63.3)	73 (63.5)	82 (68.3)
South America	11 (9.2)	10 (8.7)	11 (9.2)
Oceania	2 (1.7)	0 (0)	2 (1.7)
Country income			
Low	5 (4.2)	7 (6.1)	5 (4.2)
Middle	49 (40.8)	37 (32.2)	42 (35.0)
High	66 (55.0)	71 (61.7)	73 (60.8)

Values are *n* (%).

The remaining 3039 patients were included in the primary analysis. Patient characteristics and operative variables according to timing of data collection (before or after intervention) are summarized in *Tables 2* and *3*, and detailed by sequence and batch in *Tables S3–S6*.These represent patient and operative risk factors for anastomotic leak, identifiable before or during surgery; they were evenly distributed before and after intervention. Demographics and operative factors for patients excluded from the primary analysis appeared representative of the whole population (*Table S7*). This study represents a high-risk population; 1354 of 3268 patients (41.4 per cent) had an ASA grade of III–V, 663 (20.3 per cent) had diabetes, 694 (21.2 per cent) had emergency operations, and there were 2540 operations for cancer (78.0 per cent).

Some 4411 surgeons were invited to undertake the intervention; 2774 (62.9 per cent) surgeons started and 2143 (48.6 per cent) completed the online training and registered for a certificate. A further 393 anaesthetists and 393 theatre staff also took part in the study. The median number of surgical team members participating in each hospital was 7 (i.q.r. 5–21, range 1–54).

Primary outcome

The absolute anastomotic leak rate was 10.1 per cent (170 of 1691) during data collection before the intervention and 9.6 per cent (129 of 1348) in the data collection interval after the intervention (*Fig. 5*). The pooled OR obtained from a mixed logistic regression analysis of each batch of clusters, adjusting for time interval, was 0.87 (95 per cent c.i. 0.59 to 1.30; $P = 0.498$) (*Fig. 5*). This confidence interval was wide and included 1.0, although it did rule out a reduction of more than 40 per cent in the odds of anastomotic leak as a result of the intervention.

Secondary outcomes

As with the primary outcome, confidence intervals for intervention effects on secondary outcomes were wide (*Tables 4*, *S8*, and *S9*) but ruled out reductions of more than 40 per cent in the odds of death, readmission, reoperation, unplanned ICU admission, stoma without primary anastomosis, and longer hospital stay.

Subgroup analyses

Results of subgroup analyses are shown *Fig. 6*, with ORs for hospital- and patient-level factors. Further details can be found in *Tables S10–S22* and *Fig. S5*. The intervention effect was modified by the proportion of surgeons in a hospital team completing online educational modules (team engagement). Anastomotic leak rates before and after intervention were 8.3 and 13.8 per cent respectively in hospitals with low team engagement (less than 50 per cent) (adjusted OR 2.09, 95 per cent c.i. 1.31 to 3.31); 10.5 and 10.2 per cent in hospitals with intermediate team engagement (50–79 per cent) (adjusted OR 0.94, 0.55 to 1.62); and 12.2 and 5.1 per cent in those with high team engagement (at least 80 per cent) (adjusted OR 0.36, c.i. 0.20 to 0.64) (P for interaction < 0.001). This interaction suggests that there was a reduction in anastomotic leak rate as a result of the intervention at hospitals with the highest level of engagement, although it also suggests an increase in

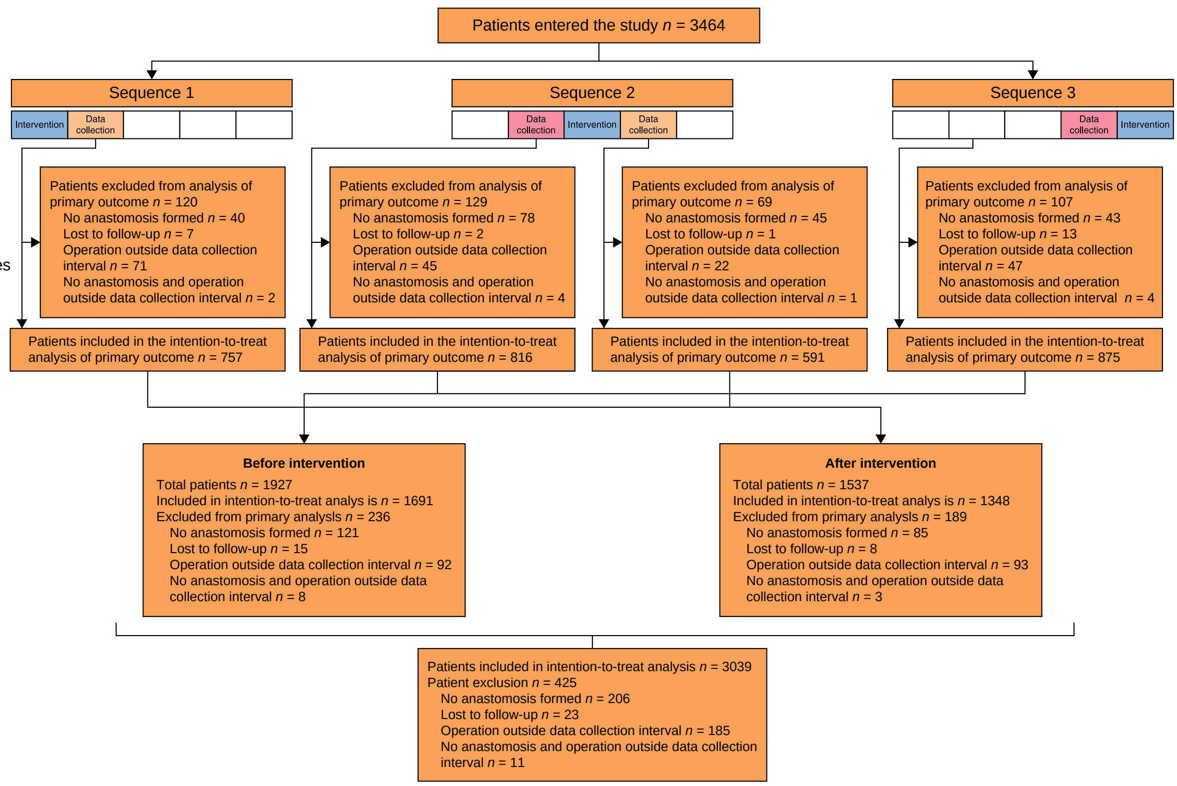

Fig. 4 Patient-level CONSORT diagram

Table 2 Patient characteristics by timing of intervention relative to surgery

	Surgery before intervention $n = 1827$	Surgery after intervention $n = 1441$	Total $n = 3268$
Age (years), median (i.q.r., range)	68 (56–77, 1–100)	68 (56–77, 2–95)	68 (56–77, 1–100)
Sex			
Male	951	738	1689
Female	874	701	1575
BMI > 30 kg/m^2			
No	1455 (80.3)	1146 (79.6)	2601 (80.0)
Yes	357 (19.7)	293 (20.4)	650 (20.0)
Known diabetes			
No	1444 (79.1)	1159 (80.5)	2603 (79.7)
Yes	382 (20.9)	281 (19.5)	663 (20.3)
History of IHD or stroke			
No	1439 (78.9)	1170 (81.2)	2609 (79.9)
Yes	385 (21.1)	271 (18.8)	656 (20.1)
Smoking status			
Never smoked	1199 (65.9)	978 (68.3)	2177 (67.0)
Ex-smoker (stopped > 6 weeks ago)	372 (20.5)	285 (19.9)	657 (20.2)
Current smoker or stopped < 6 weeks ago	248 (13.6)	168 (11.7)	416 (12.8)
Oral anticoagulants			
No	1540 (84.7)	1229 (85.5)	2769 (85.0)
Yes	279 (15.3)	208 (14.5)	487 (15.0)
Preoperative total protein level (g/dl)			
≤ 4.5	128 (7.8)	81 (6.1)	209 (7.1)
4.5–5.5	360 (22.0)	273 (20.7)	633 (21.4)
6.0–7.5	1068 (65.1)	905 (68.6)	1973 (66.7)
≥ 8.0	84 (5.1)	61 (4.6)	145 (4.9)
Preoperative haemoglobin (g/dl)			
< 60	22 (1.2)	23 (1.6)	45 (1.4)
60–89	175 (9.6)	160 (11.1)	335 (10.3)
90–119	821 (45.3)	607 (42.3)	1428 (44.0)
120–139	534 (29.4)	415 (28.9)	949 (29.2)
≥ 140	262 (14.4)	230 (16.0)	492 (15.1)

Values are *n* (%) unless otherwise indicated. IHD, ischaemic heart disease.

Table 3 Operative factors by timing of intervention

	Surgery before intervention $n = 1827$	Surgery after intervention $n = 1441$	Total $n = 3268$
Timing of surgery			
Elective (planned)	1221 (66.8)	1004 (69.7)	2225 (68.1)
Expedited (within 2 weeks of decision)	205 (11.2)	144 (10.0)	349 (10.7)
Emergency (unplanned)	401 (21.9)	293 (20.3)	694 (21.2)
Indication for surgery			
Malignancy	1399 (76.7)	1141 (79.6)	2540 (78.0)
Inflammatory bowel disease	171 (9.4)	103 (7.2)	274 (8.4)
Other	253 (13.9)	190 (13.2)	443 (13.6)
Bowel preparation			
None	414 (22.7)	274 (19.1)	688 (21.1)
Mechanical bowel preparation only	322 (17.7)	272 (18.9)	594 (18.2)
Mechanical bowel preparation with oral antibiotics	1086 (59.6)	892 (62.0)	1978 (60.7)
ASA grade[25]			
I	217 (12.0)	160 (11.2)	377 (11.6)
II	838 (46.4)	669 (46.8)	1507 (46.5)
III	653 (36.1)	534 (37.3)	1187 (36.7)
IV	88 (4.9)	64 (4.5)	152 (4.7)
V	11 (0.6)	4 (0.3)	15 (0.5)
Primary operating surgeon			
Consultant colorectal surgeon	934 (51.2)	764 (53.1)	1698 (52.0)
Trainee colorectal surgeon	210 (11.5)	188 (13.1)	398 (12.2)
Consultant general surgeon	465 (25.5)	338 (23.5)	803 (24.6)
Trainee general surgeon	215 (11.8)	150 (10.4)	365 (11.2)
Most senior surgeon in theatre			
Consultant colorectal surgeon	1188 (65.0)	950 (65.9)	2138 (65.4)
Trainee colorectal surgeon	38 (2.1)	44 (3.1)	82 (2.5)
Consultant general surgeon	494 (27.0)	378 (26.2)	872 (26.7)
Trainee general surgeon	107 (5.9)	69 (4.8)	176 (5.4)
Operative approach			
Open	883 (48.3)	643 (44.6)	1526 (46.7)
Laparoscopic (completed)	762 (41.7)	650 (45.1)	1412 (43.2)
Laparoscopic (converted to open)	133 (7.3)	121 (8.4)	254 (7.8)
Robotic (completed)	47 (2.6)	26 (1.8)	73 (2.2)
Robotic (converted to open)	2 (0.1)	1 (0.1)	3 (0.1)
Operative field contamination*			
Clean-contaminated	1586 (87.0)	1258 (87.4)	2844 (87.2)
Contaminated	158 (8.7)	125 (8.7)	283 (8.7)
Dirty	79 (4.3)	56 (3.9)	135 (4.1)

Values are *n* (%). *Centers for Disease Control and Prevention[26]; definition in *Appendix S1*.

anastomotic leak rate at hospitals with the lowest engagement—something that was not hypothesized. Team engagement was lower in hospitals involved later in the trial (*Fig. S5*).

There was no evidence of an interaction of the intervention effect with number of hospital beds, right colectomy volume, early *versus* late involvement in the trial, health service expenditure, or World Bank income group, at participant level, indication, urgency, ASA grade, operative approach, anastomosis formation technique, primary operating surgeon grade, or primary operating surgeon specialism.

Sensitivity analyses

Per-protocol sensitivity analysis was also conducted for the primary outcome in patients in whom all three intervention components (training, risk stratification, and checklist) were completed (OR 0.84, 95 per cent c.i. 0.53 to 1.31; $P = 0.439$) (*Fig. S6* and *Tables S23–S28*).

Clusters from randomization batches 1 and 2 were paused owing to the COVID-19 pandemic and restarted when ready. Details have been published[15]. Because of this disruption, a sensitivity analysis was performed, after exclusion of batches 1 and 2 (OR 0.85, 0.56 to 1.30; $P = 0.461$) (*Fig. S7*).

Discussion

The EAGLE trial did not find conclusive evidence for a reduction in anastomotic leak rates following the intervention, although a subgroup analysis did identify a reduction in leak rates in hospital teams with high team engagement in the intervention. This may reflect better knowledge, better decision-making, and more engaged team performance through enhancement of non-technical skills.

This complex intervention required the participation of a multidisciplinary team of surgeons, nurses, and anaesthetists to implement practice change within a hospital. It cannot be ignored that the EAGLE trial was carried out when team function was being severely challenged by the COVID-19 pandemic. There was evidence of reduced team engagement in the later randomization batches (*Fig. S5*), reflecting surgical services struggling during the recovery phase of the pandemic. This clinical challenge was reported widely[27–29], being explained by the overwhelming demand on restarting elective surgical services. This also coincided with a rising baseline of anastomotic leaks during this phase of the EAGLE trial (*Table S12*), perhaps reflecting the significant challenges faced by surgeons at this time and more advanced disease resulting from delayed patient presentation.

Quality improvement can be an important tool for hospital teams. Examples such as the WHO Surgical Safety Checklist[30] and the INTERACT3 trial[31] have improved patient outcomes. It is being increasingly recognized that low-standard quality improvement needs to be avoided[7], but that high-standard quality improvement will need lighter-touch, digital processes (INTERACT3 and EPOCH[31,32]). Dissemination and uptake of new tools, such as the WHO Trauma Checklist[33], could benefit from such evaluation. The EAGLE online quality improvement intervention was accessed by 2774 surgeons across 5 continents in 332 hospital teams, changing clinical practice across 3 continents. The methodology was highly efficient, able to be delivered at scale and speed. EAGLE incurred no direct costs for participants and was exceptionally affordable. This global multicentre RCT was delivered at a total cost of Euros 460 000. The digital format of the intervention and global generalizability represent a substantial shift towards democratizing education and quality. The team structures used to deliver the study, and the inclusion of anaesthetists, nurses, as well as surgeons, supported its distribution and proved essential to its implementation. Challenges with cultural and language barriers were overcome, leading to the intervention being broadly

Batch	Anastomotic leak rate: Surgery after intervention	Anastomotic leak rate: Surgery before intervention	Weight (%)	OR	OR
1	10 of 117	22 of 247	7.8	1.13 (0.27, 4.68)	
2	15 of 116	5 of 40	5.7	0.87 (0.17, 4.54)	
3	10 of 153	13 of 115	8.3	0.54 (0.14, 2.13)	
4	5 of 103	12 of 125	7.0	0.49 (0.11, 2.20)	
5	4 of 81	17 of 150	6.8	0.55 (0.12, 2.53)	
6	6 of 84	9 of 96	6.8	0.98 (0.21, 4.49)	
7	6 of 87	5 of 117	4.8	0.49 (0.08, 3.03)	
8	8 of 96	14 of 149	6.7	0.33 (0.07, 1.52)	
9	5 of 50	8 of 76	4.0	0.85 (0.12, 6.10)	
10	11 of 59	10 of 63	7.7	0.94 (0.23, 3.90)	
11	4 of 59	7 of 80	3.1	3.07 (0.32, 29.21)	
12	10 of 76	8 of 80	6.5	2.68 (0.57, 12.73)	
13	12 of 62	9 of 99	7.9	2.71 (0.66, 11.14)	
14	4 of 68	14 of 79	4.6	0.19 (0.03, 1.20)	
15	4 of 56	7 of 79	5.9	0.81 (0.16, 4.18)	
16	15 of 81	10 of 99	6.3	1.76 (0.36, 8.55)	
Total	129 of 1348	170 of 1691	100.0	0.87 (0.59, 1.30)	

Test for overall effect: *Z* = –0.677, *P* = 0.498

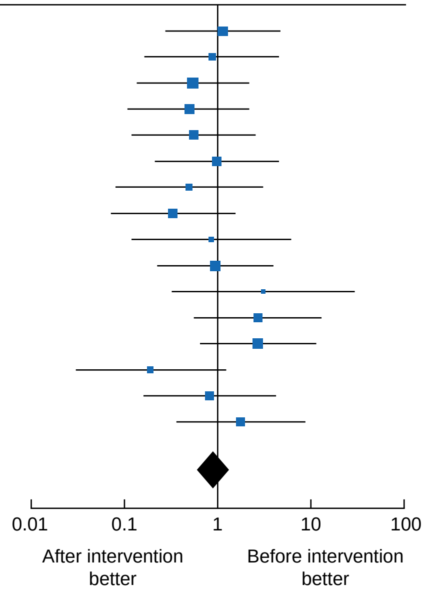

Fig. 5 Forest plot showing effect of intervention on anastomotic leak rate

Meta-analysis was conducted across all 16 batches of the study. Each batch was analysed using a mixed-effects logistic regression model adjusting for hospital number of beds, country income, type of hospital (referral *versus* non-referral), sex, urgency, and data collection interval. Hospital was included as a random effect. Overall effect pooled in a random-effects meta-analysis using the inverse-variance approach of DerSimonian and Laird[23]. ORs are shown with 95% confidence intervals.

Table 4 Effect of intervention on secondary outcomes, analysed across all batches

	Surgery before intervention	Surgery after intervention	OR*	P
Clinical leak				
No	1594 of 1689 (94.4)	1287 of 1348 (95.5)		
Yes	95 of 1689 (5.6)	61 of 1348 (4.5)	0.77 (0.53, 1.12)	0.165
Missing	17	8		
Death				
No	1727 of 1802 (95.8)	1375 of 1432 (96.0)		
Yes	75 of 1802 (4.2)	57 of 1432 (4.0)	1.02 (0.70, 1.49)	0.906
Missing	25	9		
Reoperation				
No	1668 of 1804 (92.5)	1332 of 1432 (93.0)		
Yes	136 of 1804 (7.5)	100 of 1432 (7.0)	0.94 (0.70, 1.26)	0.667
Missing	23	9		
Readmission				
No	1680 of 1804 (93.1)	1351 of 1432 (94.3)		
Yes	124 of 1804 (6.9)	81 of 1432 (5.7)	0.90 (0.64, 1.26)	0.523
Missing	23	9		
Duration of hospital stay (days)				
≤ 10	1327 of 1800 (73.7)	1044 of 1424 (73.3)		
> 10	473 of 1800 (26.3)	380 of 1424 (26.7)	1.02 (0.82, 1.27)	0.881
Missing	27	17		
Unplanned admission to ICU				
No	1735 of 1802 (96.3)	1381 of 1427 (96.8)		
Yes	67 of 1802 (3.7)	46 of 1427 (3.2)	0.95 (0.61, 1.46)	0.803
Missing	25	14		
Stoma without primary anastomosis				
No	1703 of 1824 (93.4)	1354 of 1439 (94.1)		
Yes	121 of 1824 (6.6)	85 of 1439 (5.9)	0.96 (0.67, 1.39)	0.829
Missing	3	2		
Defunctioning ileostomy with primary anastomosis				
No	1772 of 1821 (97.3)	1413 of 1436 (98.4)		
Yes	49 of 1821 (2.7)	23 of 1436 (1.6)	0.71 (0.34, 1.49)	0.364
Missing	6	5		
Any stoma formation				
No	1654 of 1827 (90.5)	1331 of 1441 (92.4)		
Yes	170 of 1827 (9.3)	108 of 1441 (7.5)	0.89 (0.62, 1.27)	0.532
Missing	3	2		

Values are *n* (%) unless otherwise indicated; *values in parentheses are 95% confidence intervals. ORs and *P* values were estimated from a three-level mixed-effects logistic regression model adjusting for hospital number of beds, country income, type of hospital (referral *versus* non-referral), sex, urgency, and data collection interval. Hospital and batch were included as random effects, with hospital nested within batch. Results split by batch are available in *Tables S8 and S9*.

	Anastomotic leak rate			
	Surgery before intervention	Surgery after intervention	Adjusted OR	P (interaction)
No. of hospital beds (h)				
< 500	71 of 643 (11.0)	44 of 461 (9.5)	0.84 (0.52, 1.36)	
≥ 500	99 of 1048 (9.5)	85 of 887 (9.6)	1.08 (0.74, 1.57)	0.427
Right colectomy voloume (no. of patients) (h)				
< 10	55 of 587 (9.4)	50 of 508 (9.8)	1.07 (0.61, 1.88)	
≥ 10	115 of 1104 (10.4)	79 of 840 (9.4)	0.95 (0.65, 1.38)	0.728
Adoption (h)				
Early batch (1–8)	97 of 1036 (9.4)	64 of 837 (7.7)	0.76 (0.51, 1.14)	
Late batch (9–16)	73 of 655 (11.2)	65 of 511 (12.7)	1.32 (0.86, 2.03)	0.065
Health service expenditure (h)				
Low	21 of 120 (17.5)	14 of 112 (12.5)	0.74 (0.31, 1.78)	
Middle	27 of 291 (9.3)	20 of 179 (11.2)	1.26 (0.60, 2.62)	0.833
Top	122 of 1280 (9.5)	95 of 1057 (9.0)	0.97 (0.69, 1.36)	
World bank income group (h)				
Low/middle	60 of 512 (11.7)	37 of 366 (11.7)	0.88 (0.52, 1.48)	
High	110 of 1179 (9.3)	92 of 982 (9.4)	1.03 (0.72, 1.48)	0.615
Proportion of surgeons completing modules (%) (h)*				
Low (< 50)	59 of 714 (8.3)	61 of 443 (13.8)	2.09 (1.31, 3.31)	
Intermediate (50–79)	50 of 477 (10.5)	44 of 432 (10.2)	0.94 (0.55, 1.62)	< 0.001
High (≥ 80)	61 of 500 (12.2)	24 of 473 (5.1)	0.36 (0.20, 0.64)	
Indication for surgery (p)				
Benign	54 of 347 (15.6)	29 of 246 (11.8)	0.70 (0.40, 1.22)	
Malignant	114 of 1340 (8.5)	100 of 1095 (9.1)	1.13 (0.81, 1.58)	0.130
Procedure urgency (p)				
Elective	106 of 1194 (8.9)	75 of 980 (7.7)	0.91 (0.63, 1.30)	
Emergency/expedited	64 of 497 (12.9)	54 of 368 (14.7)	1.13 (0.72, 1.77)	0.438
ASA grade (p)				
I–II	88 of 995 (8.8)	64 of 792 (8.1)	0.96 (0.65, 1.41)	
III–V	79 of 681 (11.6)	64 of 546 (11.7)	1.04 (0.69, 1.57)	0.772
Operative approach (p)				
Open	124 of 902 (13.8)	88 of 689 (12.8)	0.93 (0.66, 1.31)	
Laparoscopic/robotic	46 of 789 (5.8)	41/659 (6.2)	1.13 (0.69, 1.84)	0.507
Anastomotic technique (p)				
Stapled	99 of 1084 (9.1)	83/863 (9.6)	1.07 (0.74, 1.54)	
Handsewn	71 of 604 (11.8)	45 of 483 (9.3)	0.82 (0.52, 1.31)	0.361
Primary operating surgeon grade (p)				
Trainee	38 of 369 (10.3)	33 of 301 (11.0)	1.17 (0.66, 2.05)	
Consultant	132 of 1319 (10.0)	96 of 1046 (9.2)	0.93 (0.67, 1.30)	0.487
Primary operating surgeon specialism (p)				
General	84 of 604 (13.9)	55 of 439 (12.5)	1.00 (0.65, 1.55)	
Colorectal	86 of 1084 (7.9)	74 of 908 (8.2)	0.99 (0.68, 1.44)	0.959

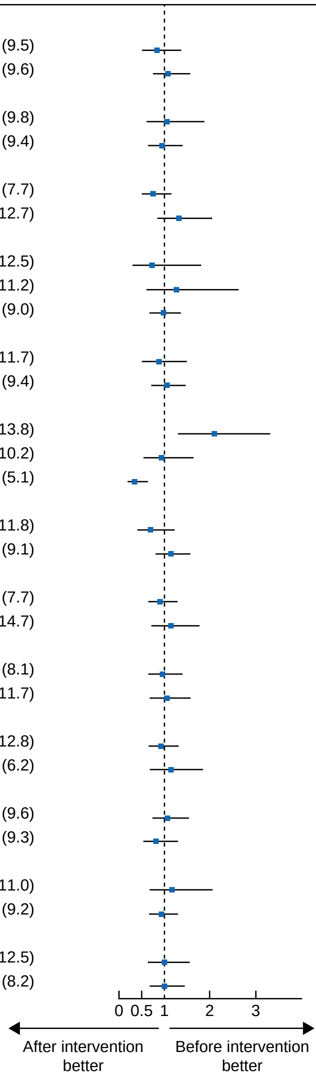

Fig. 6 Subgroup analyses of primary outcome, analysed across all batches

ORs and *P* values were estimated from a three-level mixed-effects logistic regression model adjusting for hospital number of beds, country income, type of hospital (referral *versus* non-referral), sex, urgency, and data collection interval. Hospital and batch were included as random effects, with hospital nested within batch. *Proportion of surgeons in each hospital-team completing online modules during the implementation of the intervention. Values in parentheses are percentages unless indicated otherwise; ORs are shown with 95% confidence intervals. h, Hospital-level factors; p, patient-level factors. Results split by batch are available in *Tables S10–S22*.

accepted across four continents, but there was a universal need to optimize engagement across hospital teams. Implementation was greatly enabled by the batched randomization process, allowing the management team to shift focus from one batch of clusters to the next and preventing collapse of the trial during the pandemic. These methods could be used by researchers targeting improvement in other common health-related topics and should be widely available[31].

EAGLE was co-developed iteratively by a multinational, multidisciplinary network that used expertise from both clinical and industry backgrounds. These factors may have helped in ensuring relevance, promoting engagement, and imparting ownership for all members of the team with a focus on optimizing patient care. Online modules can be viewed at the learner's speed to allow for differences in language fluency, time available, and surgeon experience. Upon trial completion, all EAGLE interventions are being made globally accessible and open access (https://eagle-escp.eu.com/).

There were limitations to this study. The COVID-19 pandemic required it to be suspended for 5 months during the initial lockdown. The pandemic had a devastating effect on elective surgery worldwide and often halted non-COVID research activity[29]. The global changes in surgical patient flow created imbalances whereby some hospitals ceased elective surgery altogether and had to withdraw from the study. The flexibility of the methodology was a key element in its successful completion. However, the pandemic did have a temporal impact on the study. Reduced engagement with the intervention within hospital teams was detected in the later batches (9–16) of the study (*Fig. S5*). There was inconsistency in the uptake of educational modules in different hospital teams. Not all registered surgeons in each department started the modules, and not all who started the modules completed them. There was also evidence of variation in impact across different cultures and languages. Qualitative studies will explore how this might be improved.

The EAGLE training modules can help underpin best clinical practice across the world and might help deliver additional non-technical benefits, notably in hospitals with high levels of team engagement. The intervention is generalizable and cross-cultural, and the study methodology and delivery are applicable to diverse clinical settings. The authors recommend that new surgeons and established surgical teams around the world consider undertaking the EAGLE training modules.

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online. This includes translations of the Abstract into Chinese, Spanish, Korean, Portuguese, and Italian.

Data availability

Data sharing requests will be considered by the management group upon written request to the corresponding author.

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