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Synopsis

Intraoperative Fluorescence Angiography to Prevent Anastomotic Leak in Rectal Cancer Surgery: a synopsis of the IntAct trial

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Abstract

Background: Anastomotic leak is the most feared complication of rectal cancer surgery, being reported in 10–15% of patients. Indocyanine green near-infrared angiography has been introduced to evaluate anastomotic blood supply and reduce anastomotic leak, with promising results.

Objective and main outcome measure: The primary objective was to evaluate the efficacy and mechanism of indocyanine green near infrared angiography in reducing the anastomotic leak rate in rectal cancer surgery. The primary end point was clinical anastomotic leak rate within 90 days of operation. The key secondary end point was the rate of all anastomotic leaks within 90 days of operation.

Design and methods: A prospective, unblinded, parallel-group, non-Clinical Trial of an Investigational Medicinal Product, randomised controlled trial comparing surgery with indocyanine green near infrared angiography against standard care (white light laparoscopy) to determine the effect on anastomotic leak in patients undergoing elective rectal cancer resection. Participants were randomised 1 : 1 using minimisation with a random element. Analyses were intention-to-treat.

Setting: Twenty-eight European hospitals.

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Participants: Adult patients ≥ 18 years with a diagnosis of rectal cancer, suitable for curative resection by high or low anterior resection with anastomosis.
Interventions: Surgery with indocyanine green near infrared angiography or standard of care.
Results: Between 10 January 2018 and 15 August 2023, 766 participants were randomised; 698 (91.1%) participants were included in the primary analysis. The overall rates of clinical and all anastomotic leaks were 90/698 (12.9%) and 121/698 (17.3%), respectively. In the primary analysis, clinical anastomotic leaks occurred in 36/343 (10.5%) and 54/355 (15.2%) in the indocyanine green near-infrared angiography and standard care groups, respectively; the primary model estimated an adjusted odds ratio of 0.667 (95% confidence interval 0.419 to 1.060; $p = 0.0868$). Key secondary analysis, including all anastomotic leaks, observed 47/343 (13.7%) and 74/355 (20.8%) leaks in indocyanine green near-infrared angiography and standard care groups, respectively, with the key secondary model estimated an adjusted odds ratio of 0.607 (95% confidence interval 0.403 to 0.915; $p = 0.0172$) in favour of indocyanine green near infrared. In the economic analysis, indocyanine green near infrared angiography had a 62% chance of being cost-effective and led to a per-patient cost saving of £97.34 (95% confidence interval £91.32 to £103.00).
Limitations: Surgeons or data collectors were unable to be blinded. The trial population largely consisted of White ethnic groups, and so some ethnic groups are likely under-represented.
Conclusions: The use of indocyanine green near infrared angiography reduces the rate of clinical and all anastomotic leaks following rectal cancer resection, but only reached statistical significance for all leaks. It is safe, easy to use and cost-effective. Taken in context with other clinical trials, our results suggest that indocyanine green near infrared angiography should be considered as the future standard of care in rectal cancer surgery.
Future work: The microbiome substudy has shown important shifts in the microbiome profile across the rectal cancer treatment pathway that warrant further investigation regarding a causal role in anastomotic leak and other postoperative complications.
Further work is required to standardise and quantify indocyanine green near infrared angiography as a means of real-time assessment of tissue perfusion.
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Introduction

This report details the work undertaken to evaluate the clinical and cost-effectiveness of intraoperative indocyanine green near-infrared (ICG-NIR) perfusion angiography in reducing anastomotic leak following rectal cancer surgery in the Intraoperative Fluorescence Angiography to Prevent Anastomotic Leak (AL) in Rectal Cancer Surgery (IntAct) trial. Quality of life (QoL) and functional bowel outcomes were included along with a cost-effectiveness evaluation. A substudy explored changes in the gut microbiome across the rectal cancer treatment pathway. The IntAct trial was funded by The National Institute for Health and Care Research, through its Efficacy and Mechanism Evaluation programme.

Background

Anastomotic leak is one of the commonest and most feared complications of rectal cancer surgery, reported to occur in 10–15% of cases and associated with a mortality of 5–10%. Patients who survive an AL not only suffer the immediate morbidity of the leak but experience long-term consequences. Bowel function is poor with a high rate of permanent stoma formation. There is an increased risk of cancer recurrence and worse overall cancer survival. Patients suffer the financial consequences of ongoing morbidity with negative effects on mental wellbeing. AL also has a significant impact on healthcare systems, more than tripling the length of hospital stays as well as the cost of care. AL rates have remained unchanged despite advances in surgical technique and perioperative care.

Rationale

A key factor in anastomotic healing is maintaining an adequate blood supply to the bowel ends, which relies upon assessing the colour of the bowel, pulsatile flow in the arterial supply, and bleeding from the cut bowel ends during surgery. This is subjective and dependant on several patient and technical factors. ICG-NIR perfusion angiography has recently been used for intraoperative assessment of anastomotic blood supply and has shown promise in reducing AL rates. Most of the evidence in support of the use of ICG-NIR is derived from small, single-centre, observational studies or systematic reviews based on the same evidence. A few randomised trials comparing ICG-NIR with white light laparoscopy have been published and show mixed results. This probably reflects the study designs, with the inclusion of mixed cohorts of participants with benign and malignant disease, and right and left colon and rectal cancers.

Although ICG-NIR might reduce the risk of AL, it does not prevent a leak from occurring, suggesting that factors other than blood supply are important. Recent attention has focused on the role of the gut microbiome as an infective cause for AL. To date, the role of the microbiome as a cause of AL has only been explored in small animal models. The results have been promising, opening opportunities for therapeutic manipulation of the gut microbiome to prevent the risk of AL. The hypothesis that the gut microbiome changes across the treatment pathways and might be causative in AL now needs to be explored in humans.

Because the risk of AL is greatest in patients undergoing rectal cancer surgery, and the consequences are proportionately greater for patients and healthcare providers, we investigated the role of ICG-NIR in this patient population. We were interested in ALs that were clinically evident as well as those that were detected as incidental findings on clinical follow-up (FU) but nevertheless can still have an adverse effect on patient outcomes. We included a health economic evaluation from an NHS perspective, which we believe is important to policy makers and healthcare providers when considering wider uptake and adoption.

Objectives

The aim of IntAct was to investigate the efficacy and mechanism of intraoperative ICG-NIR perfusion angiography in reducing AL rate following elective rectal cancer surgery compared to standard white light laparoscopy, using either a laparoscopic or robotic technique. The target population was patients aged 18 or over with a diagnosis of rectal cancer that were suitable for curative resection by high or low anterior resection.

The primary trial objective was to assess whether surgery with ICG-NIR reduced AL rate following rectal cancer surgery, compared to standard care.

Secondary trial objectives included whether surgery with ICG-NIR, compared to standard care:

1. Altered intraoperative decision-making with regards to anastomosis construction.
2. Resulted in reduced stoma rates (temporary or permanent).
3. Improved patients' QoL.
4. Resulted in cost savings for the NHS.

Substudy objectives were:

1. Microbiome substudy: To assess changes in the rectal microbiome across the treatment pathway and its association with AL.
2. Perfusion substudy: To evaluate rectal vascular anatomy and perfusion using computerised tomography (CT) angiography and CT perfusion imaging to allow variations in ICG-NIR to be interpreted in light of individual patient anatomy and physiology.

Methods

Full details of the IntAct trial design and analysis plan were published as a protocol.[1] Protocol amendment history is recorded in *Appendix 1*, *Table 1*.

Trial design summary

IntAct was a European, multicentre, prospective, unblinded, parallel-group, randomised controlled trial comparing surgery with ICG-NIR against standard care (white light laparoscopy) to determine the effect on AL in patients undergoing elective anterior resection for rectal cancer. Two substudies, a microbiome substudy and a perfusion substudy, were included in UK sites to explore their potential the mechanisms of AL. An economic evaluation was also conducted alongside the trial. The trial flow diagram can be found in *Appendix 2*, *Figure 1*.

It was planned that IntAct would randomise 880 participants on a 1 : 1 basis, using minimisation incorporating a random element, between surgery with ICG-NIR and standard care. Minimisation factors were intended operating surgeon, American Society of Anesthesiologists (ASA) grade, sex, preoperative T-stage, neoadjuvant therapy type, and tumour position. An interim analysis to allow the trial to stop early for efficacy was planned to occur once primary end-point data were available for 554 participants. Participants were followed up for 90 days post operation, with additional data collection at 12 months for UK participants who reached 12 months post operation within the overall IntAct FU period. The trial was not blinded to participants, medical staff, or clinical trial staff.

IntAct received national ethical approval in the UK (reference number 17/NW/0193) and either national or local ethical approval (as required) at international centres. The trial was managed by Leeds Clinical Trials Research Unit (CTRU) and overseen by an independent Trial Steering Committee (TSC) and a Data Monitoring and Ethics Committee (DMEC). IntAct was prospectively registered on the International Standard Randomised Controlled Trial Number Register, reference number ISRCTN13334746.

Participants

Eligible patients were aged 18 and older, and had a diagnosis of rectal cancer, defined as a lower margin ≤ 15 cm from the anal verge as assessed endoscopically or radiologically, and be medically fit (ASA ≤ 3) for curative

resection by high or low anterior resection. Patients of all ethnicities were eligible. Patients were ineligible if not undergoing colorectal/anal anastomosis, had synchronous colonic tumours, recurrent rectal cancer, or locally advanced rectal cancer requiring extended/multivisceral excision, coexistent colorectal pathology, previous pelvic radiotherapy unrelated to rectal cancer, hepatic or renal dysfunction, known allergy to ICG or iodine, or were immunocompromised.

Participants were recruited from 28 hospitals across 8 countries; 19 UK NHS hospitals and 9 European hospitals (see *Appendix 3*, *Table 2*). Participating centres had to be able to perform laparoscopic or robotic-assisted rectal cancer surgery with ICG-NIR and participating surgeons must have performed a minimum of three rectal cancer resections using ICG-NIR. In total, 78 surgeons recruited participants to the IntAct trial (see *Appendix 4*, *Figure 2*).

Following confirmation of written informed consent and eligibility, patients were randomised into the IntAct trial. Randomisation was performed centrally using the CTRU 24-hour randomisation service.

Interventions

All rectal cancer resections were performed according to the surgeon's usual technique, using a laparoscopic or robotic approach. High anterior resection was defined as resection and anastomosis above the peritoneal reflection, with low anterior resection defined as resection and anastomosis at or below the peritoneal reflection. Colorectal/anal anastomosis was performed according to surgeon's preference with defunctioning stoma at the surgeon's discretion.

In the standard care group, a White light assessment of bowel perfusion was performed. In the ICG-NIR group, two ICG-NIR assessments were required, each involving a bolus of 0.1 mg/kg of ICG. The first followed mobilisation of the colon and division of the rectum with the planned level of proximal bowel transection marked. Changes in the level of proximal bowel or rectal transection were recorded. The second assessment followed anastomosis. A third dose of ICG was permitted (e.g. endoluminal assessment). Deviations from the pre-planned operation (e.g. use of a defunctioning stoma) were recorded. Postoperative care was as per institutional protocol and could include enhanced recovery after surgery pathways.

Data collection

Clinical data were collected at baseline, perioperatively, and at 30 and 90 days post operation for all patients, plus at 12 months post operation for UK participants where this date fell within the 90 days following the last trial participant's operation.

Details of data collection are presented in the protocol manuscript.[1] Baseline data included patient demographics, tumour characteristics, the use of antibiotics in the previous 8 weeks, mechanical bowel preparation, and planned operation. Perioperative data included operative details, type of anastomosis, anastomotic perfusion with ICG-NIR (intervention group) or white light laparoscopy (standard care group), change in operative plan, stoma formation, intraoperative complications, and complications at 30 and 90 days post operation. Complications were classified according to Clavien–Dindo[2] and the Comprehensive Complication Index (CCI).[3] A contrast enema was mandatory between 4 and 6 weeks post operation in all patients that had not suffered an AL. QoL was recorded at baseline, 30 and 90 days (and 12 months for UK patients within the time frame of the study) using European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-30) global health, QLQ-CR29 colorectal-specific health, and EuroQol-5 Dimensions, five-level version (EQ-5D-5L) health status questionnaires. Low anterior resection syndrome (LARS) score was collected at baseline and 30 and 90 days. Health and social care resource utilisation data were collected from UK participants at baseline, at 30 and 90 days and at 12 months for patients within the time frame of the study.

Outcome measures

Primary and key secondary outcomes

Anastomotic leaks were defined, as per the International Study Group for Rectal Cancer definition,[4] as a confirmed defect of the intestinal wall at the anastomotic site (including suture and staple lines of neorectal reservoirs) leading to a communication between the intra- and extraluminal compartments. An abscess arising in proximity to an anastomosis was considered to have arisen from an AL. ALs were classified into three categories (see *Appendix 5*, *Table 3*): grade A, requiring no active therapeutic intervention; grade B, requiring active therapeutic intervention (e.g. radiological or endoscopic treatment) but manageable without relaparotomy; and grade C, requiring relaparotomy.

The primary outcome was the occurrence of clinical AL at 90 days post operation. Clinical AL was defined as grades B and C. The key secondary outcome was occurrence of any ALs (grades A, B and C) at 90 days post operation.

Secondary outcomes

Secondary clinical outcomes included changes made to the planned anastomosis, rate of stoma formation (defunctioning and permanent), intraoperative complications, postoperative complications at 30 and 90 postoperative days, reinterventions, death and length of hospital stay. Patient-reported outcomes included the EORTC QLQ-C30 global health and QLQ-CR29 colorectal-specific QoL scales, resection-specific LARS score, and health resource utilisation.

Cost-effectiveness analysis

The economic evaluation was restricted to the UK trial data and the health and personal social services perspective. Costs were estimated in UK (£) pounds (year 2023) and captured in trial case report forms (length of stay, interventions) and patient-reported health-care resource use (secondary, primary and community care use). Costs included those relating to ICG-NIR, surgical procedure, leak and related interventions, length of stay, outpatient care, primary care and medications. Unit prices were taken from the NHS cost collection and the Personal Social Services Research Unit Report. Quality-adjusted life-years (QALYs) were estimated over 3 months by combining data on survival and utility weights from the EQ-5D-5L. The EQ-5D-5L responses were mapped to the EuroQol-5 Dimensions, three-level version utility index using an approved algorithm. Analyses included incremental costs and benefits (leaks avoided and QALYs) and incremental cost-effectiveness ratios (ICERs). We adjusted costs and QALYs accounting for baseline differences and trial stratification factors. Complete case analyses and analyses imputing for missing data (using chained equations) were conducted. We estimated sampling uncertainty by taking random draws from the variance of costs and QALYs, and this uncertainty is represented as plots on the cost-effectiveness plane and cost-effectiveness acceptability curve.

Microbiome substudy (United Kingdom only)

A microbiome substudy was conducted across UK centres. This exploratory analysis aimed to assess how the rectal microbiome and bacterial collagenase activity changed in response to surgery, and their potential associations with AL. A total of 327 UK patients were eligible for inclusion when recruitment to the substudy closed in January 2023.

Rectal swabs were collected at three time points: preoperatively, on the day of surgery, and on postoperative days 3–5. Samples were analysed using two methods: (1) 16S rRNA sequencing, and (2) microbial culture to isolate and quantify bacterial collagenase production. Clinical metadata were retrieved for all patients recruited to the substudy and analysed alongside sequencing and collagenase data.

Collection of four samples at each time point was initially stipulated in the trial protocol, which included two mucosal samples, using an Oricol™ (Great Abington, Cambridge, UK) balloon system and a rectal swab, and two luminal samples using rectal swabs with a target sample size of 200 UK participants. Results from a preliminary analysis of the microbiome samples provided interesting results. Following approval from the TSC, the microbiome substudy target population was increased. The preliminary analysis also suggested that the mucosal samples yield similar results. As sites were often reluctant to use the Oricol device a decision was made to remove the requirement to collect the mucosal sample with the Oricol device, reducing the number of samples taken at each time point.

Perfusion substudy

An optional perfusion substudy involving two additional scans (computed tomography angiography and computed tomography perfusion) was initially included to explore variations in vascular anatomy and rectal perfusion in 75 UK participants recruited to the ICG-NIR group at select UK sites. This substudy proved to be unfeasible due to difficulty in integrating the additional consent and scans into the patient pathway and was removed from the trial following approval by the TSC. No participants had been recruited to the Perfusion substudy prior to its removal from the trial.

Statistical considerations

The original sample size was 880 participants, to include an interim analysis once primary end-point data were available for 554 patients. This provided 80% power at the 5% (two-sided) level of significance to detect a reduction in clinical AL rate from the assumed 12% in the standard care group to 6% in the ICG-NIR group, allowing for 10% attrition. At the interim analysis a sample size recalculation was performed, and the target sample size reduced to 766 participants based on the independent DMEC's recommendation. This recommendation was made based on a higher than assumed clinical AL rate in the standard care arm. The new estimate of the sample size was calculated using a conditional power approach, and was based on the lower confidence limit of the one-sided 90% confidence interval (CI) of the clinical AL rate in the standard care arm at the time of interim analysis of 13.63%.

Hypothesis testing for the primary end point used the O'Brien Fleming alpha spending function to maintain an overall 5% significance level across the interim and final

tests (significance threshold of $p = 0.0477$ at final analysis). Hypothesis testing on all secondary end points was only performed at the final analysis and were all conducted at the 5% significance level. All hypothesis tests were two-sided.

All analyses were pre-specified in a statistical analysis plan and were conducted on the intention-to-treat population. Complete case analyses were performed for all pre-specified end points. Modelling for all end points incorporated a random effect with respect to intended operating surgeon and adjusted for the other minimisation factors as fixed effects. Models for QoL outcomes additionally included time points as fixed effects and treatment by time point interactions were estimated.

Multilevel logistic regression was used to estimate the odds ratios (ORs) for all binary end points (clinical AL, any AL, change in planned anastomosis, intraoperative complications, and reinterventions). Additionally, multilevel ordinal logistic regression was used to estimate the ORs for stoma formation.

Multilevel generalised linear models, using normal errors and an identity link as the preliminary approach, were used to estimate the difference in mean outcome between the treatment groups for continuous end points (length of postoperative stay, EORTC global health status, and LARS score). Alternative approaches to the choice of link function and error distribution were considered based on model diagnostics, if appropriate.

Modelling of postoperative complications comprised both a multilevel logistic regression and multilevel generalised linear model in a hurdle model. These components were respectively used to estimate the OR for experiencing at least one postoperative complication using surgery with ICG-NIR versus standard care, and the difference in expected severity between the treatment groups in those patients who had at least one complication.

Subgroup analyses explored any potential interactions between treatment allocation and stratification factor effects on clinical AL.

The primary and key secondary analysis models were refitted using the corrected stratification factors, actual operating surgeon, and the treatment actually received, to assess the robustness of the analysis conclusions.

A mediation analysis was performed to evaluate the effect of treatment allocation on the use of defunctioning stoma (the mediator) and its subsequent effect on AL.

Results

Recruitment

Between 2017 and 2023, 2534 patients were assessed for eligibility for IntAct with 1766 subsequently excluded. From 28 European sites, 766 participants were recruited and 383 were randomised to each group. Recruitment rates varied across participating sites, ranging from 1 to 5 participants recruited at the lowest recruiting sites, to 132 at the highest. The study population was representative of a Western cohort of patients with rectal cancer. Most participants were male, ASA grade II, with cancers staged T2/3 being most common. Key baseline characteristics are presented in *Appendix 6*, *Table 4*.

Intention-to-treat analysis was performed on the 698 participants with complete data for the primary and key secondary outcomes. Participant flow throughout the trial is shown in the Consolidated Standards of Reporting Trials (CONSORT) diagram (see *Appendix 6*, *Figure 3*).

Main trial outcomes

Further details of all of the analyses summarised below are in the main results manuscript.[5]

Primary and key secondary outcome

The full models and associated summary of the analysis variable (ALs by grade and treatment group) are presented in *Appendix 6*, *Table 5*. For the primary outcome, clinical ALs (grades B and C) occurred in 90/698 (12.9%) overall; 36/343 (10.5%) in the ICG-NIR group, and 54/355 (15.2%) in the standard care group. The estimated adjusted OR of clinical AL using ICG-NIR compared to standard care was 0.667 (95% CI 0.419 to 1.060; $p = 0.0868$), with an estimated 33.3% (95% CI −6.0% to 58.1%) reduction in the odds of experiencing a clinical AL with ICG-NIR. The treatment effect estimate of surgery with ICG-NIR did not meet the pre-specified significance threshold of 0.0477, and therefore a statistically significant result for the primary end point was not observed. However, there still existed a strong treatment effect in favour of ICG-NIR, despite failing to reach statistical significance. For the key secondary outcome, any AL (grades A, B or C) occurred in 121/698 (17.3%) overall; 47/343 (13.7%) in the ICG-NIR and 74/355 (20.8%) in the standard care groups. The estimated adjusted OR of AL in the ICG-NIR as compared to the standard care group was 0.607 (95% CI 0.403 to 0.915; $p = 0.0172$), with an estimated 39.3% (95% CI 8.5% to 59.7%) reduction in the odds of experiencing any AL in the ICG-NIR group. Therefore, surgery with ICG-NIR reduced the proportion of participants experiencing an AL of any grade within 90 days of trial surgery

when compared to standard of care, after adjusting for the minimisation factors.

Subgroup analyses found no clear evidence of interactions between treatment and any of the minimisation factors (intended operating surgeon, sex, ASA grade, radiological T-stage, neoadjuvant therapy, tumour position).

The mediator analysis found no evidence to suggest that the impact of use of ICG-NIR on AL is mediated by its impact on the decision to perform a defunctioning stoma. Specifically, use of ICG-NIR did not appear to impact the decision to perform a defunctioning stoma.

The sensitivity analysis using treatment actually received rather than intention-to-treat patient groups did not meaningfully change the conclusions regarding the effectiveness of ICG-NIR.

Other secondary outcomes

Key results for secondary outcomes are presented in *Appendix 6*, *Table 6*. Please note that analyses of secondary endpoints were not statistically powered. Changes in planned anastomosis occurred in 73/751 (9.7%) overall; 47/377 (12.5%) in the ICG-NIR and 26/374 (7.0%) in the standard care groups. More participants in the ICG-NIR than the standard care group underwent a change in the proximal level of bowel transection (6.7% vs. 3.0%) or stoma formation (5.0% vs. 2.4%), with no statistically significant difference in change to the rectal transection level. This resulted in a strong treatment effect of surgery with ICG-NIR as compared to standard care, with modelling showing an estimated adjusted OR of change in planned anastomosis of 2.152 (95% CI 1.251 to 3.699; $p = 0.0057$).

Postoperative stoma presence was common, occurring in 238/377 (63.1%) in the surgery with ICG-NIR and 236/374 (63.1%) in the standard care groups. The estimated adjusted OR of stoma presence versus no stoma presence at 90 postoperative days in the surgery with ICG-NIR group as compared to standard care was 1.163 (95% CI 0.848 to 1.595; $p = 0.3494$). Likewise, the OR of permanent stoma presence versus no permanent stoma (defunctioning or no stoma) is equivalent due to the proportional odds assumption.

There was no statistically significant difference in the rate of intraoperative complications [17/377 (4.5%) vs. 16/374 (4.3%) for ICG-NIR and standard care groups respectively, with estimated adjusted OR of intraoperative complication of 1.113 (95% CI 0.542 to 2.284; $p = 0.7705$)]. Incidence of postoperative complications [occurring in 145/377 (38.5%) in the surgery with ICG-NIR group and 168/374 (44.9%) in the standard care group] demonstrated an estimated adjusted OR that favoured surgery with ICG-NIR of 0.738 (95% CI 0.539 to 1.011; $p = 0.0585$), though given that a complication occurred, overall burden of complications (CCI score) was similar between groups [estimated adjusted difference in mean CCI (surgery with ICG-NIR vs. standard care) was 1.167 (95%CI −2.376 to 4.710; $p = 0.5170$)]. Reinterventions also showed no statistically significant difference between treatment groups [66/377 (17.5%) in the surgery with ICG-NIR group and 81/374 (21.7%) in the standard care group]; the estimated adjusted OR of reinterventions occurring within 90 days in the surgery with ICG-NIR as opposed to standard care was 0.761 (95% CI 0.523 to 1.107; $p = 0.1529$). Two deaths occurred in each group within 90 days.

There was no statistically significant difference in median length of hospital stay between the two groups, [median 7.0 days (range 1.0–324.0) and median 7.0 days (range 1.0–110.0) in the surgery with ICG-NIR and standard care groups, respectively]; using an alternative log-link model due to initial poor fit of the pre-specified model yielded an adjusted treatment effect estimate of 0.990 (95% CI 0.911 to 1.077; $p = 0.8177$).

Summaries of patient QoL data were presented in *Appendix 6*, *Table 7*. No statistically significant difference was observed in the EORTC-QLQ-C30 Global Health Status score between the ICG-NIR and standard care group at 30 days, 90 days and 12 months [adjusted treatment effect estimates of surgery with ICG-NIR against standard care on mean global health status score were 0.5240 (95% CI −3.1532 to 4.2013; $p = 0.7799$), −1.4955 (−4.6844 to 1.6934; $p = 0$. 0.3578) and −0.5969 (−5.1179 to 3.9241; $p = 0.7957$), for each time point, respectively]. Global Health Status score decreased in both groups at 30 days with improvement at 90 days and 12 months. Similarly, no statistically significant difference was observed in LARS score between the ICG-NIR and standard care groups [adjusted treatment effect estimates of surgery with ICG-NIR compared to standard care were 2.3022 (−1.8278 to 6.4323; $p = 0.2742$), and 0.8671 (−2.2988 to 4.0329; $p = 0.5611$) for 30 and 90 days, respectively, with worse LARS scores in both groups at 30 and 90 days as compared to baseline].

Health economics

The primary cost-effectiveness analysis using multiple imputation showed that ICG-NIR was cheaper than standard care, saving on average £97 per patient. QALYs were

roughly equivalent but with ICG-NIR leading to a negligible loss (0.001) (see *Appendix 6*, *Table 7*). The ICER was £82,011 which, given the sign on the incremental QALY, indicates the cost savings achieved with the loss of one QALY. As the ICER is above the National Institute for Health and Care Excellence threshold of £20,000–30,000 per QALY, ICG-NIR can be considered cost-effective. However, there is substantial uncertainty around the result, with ICG-NIR having a 62% chance of being cost-effective.

Further details regarding the health economics analysis are being prepared for publication.[6]

Microbiome substudy

A total of 381 rectal swabs were obtained from 202 patients across 3 time points.

At baseline, smoking status explained 3.2% of variation in beta-diversity ($p = 0.046$). On the day of surgery, beta-diversity was associated with hospital site (11.1%, $p = 0.033$), bowel preparation (2.6%, $p = 0.024$), and oral antibiotics (1.0%, $p = 0.020$). Postoperatively, beta-diversity was influenced by hospital site (16.3%, $p < 0.001$), defunctioning stoma (2.9%, $p = 0.003$) and oral antibiotics (1.6%, $p = 0.006$).

Alpha-diversity decreased as patients progressed through treatment, with postoperative increases in *Enterococcus* and *Prevotella* (see *Appendix 7*, *Figure 4A*). The presence of a defunctioning stoma was associated with lower alpha-diversity, and increased *Pseudomonas* and *Streptococcus* (see *Appendix 7*, *Figure 4B* and *C*).

No significant differences in alpha- or beta-diversity were observed between patients with and without AL (see *Appendix 7*, *Figure 5B* and *C*), although subtle differences in low abundance taxa, including *Hungatella*, *Eisenbergiella*, *Eubacterium* (see *Appendix 7*, *Figure 5A*) were detected, and 43.6% of postoperative samples demonstrated bacterial collagenase activity.

Further details regarding the microbiome analysis can be found in the published manuscript.[7]

Discussion

The IntAct study was a rigorous evaluation of rectal cancer surgery, undertaken within a pragmatic clinical trial design, and recruiting from 28 centres in Europe. It confirmed that AL is a real clinical problem with 20.8% of patients suffering some form of leak following standard care, which is higher than usually reported in the literature. Given the morbidity and mortality associated with AL, along with the financial consequences, there is an urgent need for strategies that reduce its occurrence.

The IntAct study has shown that the use of ICG-NIR reduces the rate of AL in patients undergoing elective rectal cancer resection as compared to standard white light laparoscopy. Although it failed to show a statistically significant benefit for ICG-NIR in preventing clinical AL, a strong signal was observed, and the CI around the estimate only narrowly failed to exclude an OR of no difference. The fact that the key secondary end point showed a significant benefit for ICG-NIR in preventing all ALs gives credibility to its efficacy. Further evidence of a causal relationship between the use of ICG-NIR and reduction in AL rate can be drawn from the more frequent change in the level of the proximal bowel transection, higher stoma rate, and the lower 90-day complication rate with the use of ICG-NIR. Although only a minority of participants were non-Caucasian, ICG perfusion is not influenced by skin pigmentation, and the results should be generalisable to all populations.

The main advantage of ICG-NIR appears to be in the reduction of grades A and B leaks, rather than the more severe grade C leaks. This resulted in a significant reduction in all leaks (grade A, B and C) and a lesser effect for clinical leaks (grades B and C). The importance of grade A leaks should not be underestimated as a source of long-term morbidity and poor functional outcome for patients; more patients with a grade A leak will have a permanent stoma than patients who have not suffered a leak. This finding highlights the importance of investigating for grade A leaks, which was mandated in IntAct with a contrast enema performed between 4 and 6 postoperative weeks. It is also important to follow patients for at least 90 days post operation as many grade A leaks will have a delayed presentation.

Although IntAct demonstrated a reduction in AL rate, this did not translate into a difference in QoL or LARS score between the groups and probably reflects the overall leak rate.

There is substantial uncertainty around the cost-effectiveness analysis with equivalence between ICG-NIR and standard care groups in terms of QALYs. There was a small-moderate benefit for ICG-NIR with a potential cost saving of £97 per case. Although small, across a sizeable number of patients, such savings could be substantial. Only one previous study has assessed the economics of ICG-NIR in colorectal surgery and shown it to be cost-effective depending on the rate of AL, the reduction in leak rate with use of ICG-NIR, and the cost of ICG.[8] This analysis only considered the

perspective of a major healthcare payer in Canada and relied on data published in the literature. In comparison, the IntAct analysis considered costs from an NHS provider perspective, including out-of-hospital costs, and is more likely to be an accurate reflection of the true cost-effectiveness.

The microbiome substudy was not powered to show a definite correlation between changes in the microbiome profile and AL rate. It was an exploratory study to determine how the microbiome changed across the treatment pathway and to provide insights into a putative causal link to AL. A progressive reduction in alpha-diversity was observed as patients progressed through treatment, typically a marker of a less healthy microbiome. This likely reflects disruption caused by bowel preparation, surgery, and perioperative antibiotics. Several perioperative factors influenced beta-diversity, including smoking, bowel preparation, hospital site and the presence of a defunctioning stoma. This highlights the microbiome's responsiveness to modifiable perioperative variables, which may represent targets for clinical optimisation. Overgrowth of *Pseudomonas* and *Streptococcus* species in the rectums of patients with a defunctioning stoma was an interesting and original finding, which could have implications for bowel function following stoma reversal and warrants further investigation. While small differences in microbiome composition were observed between patients with and without AL, their clinical significance remains uncertain. Notably, the detection of collagenase-producing organisms – previously implicated in AL in pre-clinical models – merits further investigation, particularly in relation to their potential for anastomotic colonisation.

Four previous randomised trials of ICG-NIR have been reported, but only one, the Japanese EssentiAL study,[9] restricted inclusion to participants with rectal cancer. There are important differences between the EssentiAL study and IntAct, including lower body mass index (BMI) in the Japanese patients, a lower overall AL rate, FU of only 30 days, and no mandating of a postoperative rectal contrast study in EssentiAL, which likely led to underreporting of AL in EssentiAL, particularly in the grade A leaks. A recent systematic review and meta-analysis of 32 studies and 11,047 patients, reported a significant benefit for ICG-NIR in reducing AL rate and, like IntAct, found a significant difference in grade A and grade B leaks, but no significant difference in grade C leaks.

The strengths of IntAct lie in its randomised and pragmatic design. The study cohort was typical of a Western population in terms of tumour characteristics and the only part of the operation that was pre-specified was assessment of anastomotic perfusion. The results are therefore likely to be generalisable to Western surgeons and healthcare systems, accepting that IntAct recruited a high proportion of patients of White ethnicity.

The limitations of IntAct include the unblinding of the surgeons and data collectors which might have introduced biases. It was not practical to standardise the method of ICG-NIR in terms of the fluorescent laparoscopic systems used, which might have introduced variability between centres. Although we attempted to eliminate the learning curve for ICG-NIR by specifying a minimum of three previous cases, it is possible that a learning curve effect was incorporated.

Patient and public involvement

Aim

The aim of patient and public involvement (PPI) in the IntAct trial was to give patients a voice, enabling them to help shape the research that set out to benefit them, and thus ensure that the trial results would be of direct relevance to the target population.

Methods and results of patient and public involvement

Patient and public involvement was an integral part of the IntAct trial from the outset. Input was sought from PPI representatives during development and review of the research proposal, feeding into the trial design. Once funding was secured, the trial had active PPI representation on the TSC throughout its duration. The TSC met prior to the start of the trial and approximately 6-monthly thereafter. Our PPI representative reviewed the trial protocol and patient-facing documents, ensuring that the trial design and participant resources were fit for purpose and appropriate for the target population. The views of our PPI representative also fed into key trial decisions, such as the decision to extend the microbiome substudy and remove the Oricol device, and to terminate the perfusion substudy. The IntAct trial continued throughout the COVID-19 pandemic. The PPI representative also provided insight, based on their experiences, into how the COVID-19 pandemic may affect trial participation.

Discussion and conclusions of patient and public involvement

Inclusion of PPI ensured the research was relevant and accessible to patients. This was done through early engagement in the trial design making sure outcomes included were important to patients as well as clinicians, and ensuring patient information appropriately addressed

patients concerns and provided information that is important to patients. PPI involvement was also critical when assessing patient burden and whether the trial pathway will be acceptable for patients. The patient perspective was integral throughout the lifetime of the trial so that patient and public opinion could be taken into account in all processes that affect patients.

Reflections and critical perspective

Designing and running this research with input from those with lived experience of the condition and the consequences of AL was invaluable. Having their unique perspective helped ensure that the trial was patient-centred, and that the results would be of utmost relevance to those the trial aimed to benefit. PPI has been only a very positive experience, and we would urge all future researchers to include PPI from the earliest possible stage of the research lifecycle.

Equality, diversity and inclusion

The IntAct trial enrolled 766 participants from 28 hospitals across 8 European countries. This wide geographical spread of participating hospitals increased the trial's scope for inclusion and diversity.

Most participants were male, from White ethnic groups, and the median age of recruited participants was 64 (range 22–89). The trial population were representative of the Western rectal cancer population reflected by the greater proportion of males recruited and distribution of participants' ASA grades, BMI, and tumour T-stages.

The reasons for the high proportion of participants enrolled from White ethnic groups are uncertain, supporting the need for additional investigation in this area.

Impact and learning

Anastomotic leaks are associated with significant burden for both patients and healthcare providers. The IntAct trial provides strong evidence that use of ICG-NIR reduces the incidence of ALs and supports its routine use in rectal cancer surgery.

The results of IntAct are likely to impact how rectal cancer surgery is performed in the NHS and wider, with strong recommendation that ICG-NIR should be standard care in the NHS. ICG-NIR is cheap, safe, and easy to use and is likely to be a cost-effective method to reduce the incidence of ALs, reducing preventable surgical morbidity and mortality and improving cancer outcomes.

The impact of the trial results may also lead to further projects to determine the efficacy of surgery with ICG-NIR for other surgical pathologies.

The microbiome substudy will determine changes in the rectal microbiome that accompany surgery, identify species associated with AL, and may lead to further studies to develop strategies to favourably influence anastomotic healing.

The results of IntAct are already having international reach, having been presented at the European Society of Coloproctology (Thessaloniki, Greece, October 2025), Asian Robotic Camp for Colorectal Surgeons (Daegu, Republic of Korea; October 2025), and Shanghai International Colorectal Cancer Symposium (Shanghai, China, October 2025).

In November 2025, the International Society for Fluorescence Guided Surgery held a webinar to present the results of the IntAct, AVOID,[10] and EssentiAL[9] trials and to discuss the implications for international clinical practice. A meta-analysis of the findings of these three studies is planned with a view to producing practice guidance aligned to the main professional colorectal surgery societies.

Implications for decision-makers

The IntAct study has shown that the use of ICG-NIR is safe and easy to use and reduces the risk of AL following rectal cancer surgery. Taken in context with other evidence, particularly that from the EssentiAL trial, and the fact that we have shown ICG-ICR to be cost-effective in reducing AL, there is a strong case that decision-makers should adopt it as standard of care.

Research recommendations

Indocyanine green near-infrared angiography

IntAct has shown that ICG-NIR provides better discrimination of bowel perfusion at an anastomosis as compared to white light laparoscopy, but ICG-NIR is still subjective. It is susceptible to operator experience and interpretation, patient characteristics (e.g. BMI), and technical issues (e.g. dose of ICG, distance of the laparoscope from the operative field, variations in intraoperative blood pressure and so on). Further research is needed to standard the ICG-NIR technique, understand the learning curve associated with its use, and to develop algorithms to quantify the intensity of the ICG fluorescent signal.

Anastomotic construction

The IntAct data set contains rich information about the technical aspects of anastomotic construction, such as the stapling technique used and the anastomotic configuration (end-to-end, side-to-end, colo-pouch etc.), which are known to influence AL and low anterior resection score and will be the subject of ongoing research.

Microbiome

The microbiome substudy has revealed interesting insights into how the gut microbiome changes across the treatment pathway of rectal cancer and the possible impact of mechanical bowel preparation and perioperative antibiotics. The reduction in microbiome diversity and the dominance of *Pseudomonas* and *Streptococcus* species in postoperative samples warrants further investigation into a causal link with AL and other postoperative complications.

Wider applications

IntAct has shown the clinical utility of ICG-NIR in assessing bowel perfusion at a colorectal anastomosis and thereby reducing the rate of AL. It is likely to have similar benefits in many other surgical applications where an adequate blood supply is critical in assessing disease severity or determining a good outcome. Examples in colorectal surgery would include assessment of inflammatory bowel disease, ischaemic bowel conditions, stoma viability and skin flaps used for anatomical reconstruction.

Conclusions

Indocyanine green near infrared angiography reduces the rate of AL following rectal cancer resection. It has a greater effect in reducing grades A and B leaks than grade C leaks, suggesting that more severe leaks are influenced by other factors in addition to adequacy of blood supply. ICG is safe and easy to use and is likely to be cost-effective. Given the burden of AL for healthcare providers and patients, the argument for not using ICG is probably no longer justified, and ICG-NIR should become standard of care in all patients undergoing rectal cancer resection.

Additional information

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

Individual participant data (with any relevant supporting material, for example data dictionary, protocol, statistical analysis plan) for all trial participants (excluding any trial-specific participant opt-outs) will be made available upon reasonable request for secondary research purposes at the end of the trial, that is usually when all primary and secondary end points have been met and all key analyses are complete and published.

Requests to access trial data should be made to CTRU-DataAccess@leeds.ac.uk in the first instance. Requests will be reviewed by relevant stakeholders. No data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention requirements, which will usually stipulate that data recipients must delete their copy of the data at the end of the planned project.

Ethics statement

IntAct received national ethical approval in the UK on 20 April 2017 from the North West – Preston Research Ethics Committee (reference number 17/NW/0193), and either national or local ethical approval (as required) at international centres.

Information governance statement

The University of Leeds (UoL) is committed to handling all personal information in line with the UK Data Protection Act (2018) and the European General Data Protection Regulation 2016/679.

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details for our Data Protection Officer here: https://ctru.leeds.ac.uk/privacy-cookies/how-we-use-personal-data/

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJDJ2014.

Primary conflicts of interest: David Jayne, Philip Quirke and Deborah Stocken are supported in part by the National Institute for Health and Care Research (NIHR) Leeds Biomedical Research Centre (NIHR213331). David Jayne, Deborah Stocken, Julie Croft, Neil Corrigan are supported in part by the NIHR Leeds HealthTech Research Centre in Accelerated Surgical Care (NIHR205280). David Jayne has previously served on the EME Prioritisation Group and the EME Strategy Group. David Meads has previously served on the HTA EESC Methods Group and the HTA EESC Panel. Philip Quirke and David Jayne are holders of NIHR Senior Investigator Awards. Deborah Stocken is a member of the EME Funding Committee and EME Advanced Fellowship Committee, and is in receipt of a NIHR Research Professorship.

We endeavour to obtain ICMJE disclosure of interests forms for all named authors. In this case, we have been unable to obtain these forms for every author. Please contact the corresponding author if you have any queries.

Department of Health and Social Care disclaimer

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN13334746.

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Award publications

This synopsis provided an overview of the research award *IntAct: Intraoperative Fluorescence Angiography to Prevent Colorectal Anastomotic Leak*.

Other articles published as part of this thread are:

Jayne D, Croft J, Corrigan N, Quirke P, Cahill RA, Ainsworth G, *et al.* Intraoperative fluorescence angiography with indocyanine green to prevent anastomotic leak in rectal cancer surgery (IntAct): an unblinded randomised controlled trial. *Lancet Gastroenterol Hepatol* 2025;**10**:806–17. https://doi.org/10.1016/S2468-1253(25)00101-3

Helliwell JA, Chilton CH, Young C, Clark EV, Wilkinson L, Fuentes Balaguer A, *et al.* Perioperative changes in the microbiome during rectal cancer surgery: exploratory analysis of the National Institute for Health and Care Research (NIHR) IntAct trial. *Br J Surg* 2025;**112**:znaf199. https://doi.org/10.1093/bjs/znaf199

The following was still under review when this synopsis was published. The following preprint version is available for the reader, please be aware this may not have been peer reviewed:

Meads DM, Vargas-Palacios A, Jayne D, Ainsworth G, Croft J, Cahill R, *et al.* Cost effectiveness of intraoperative fluorescence angiography to prevent anastomotic leak in rectal cancer surgery: economic evaluation alongside the IntAct randomized controlled trial. *medRxiv* 2025. https://doi.org/10.1101/2025.10.03.25337241

For more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/14/150/62).

About this synopsis

The contractual start date for this research was in September 2016. This synopsis began editorial review in January 2025 and was accepted for publication in October 2025. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The Efficacy and Mechanism Evaluation editors and publisher have tried to ensure the accuracy of the authors' synopsis and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this synopsis.

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List of abbreviations

AL	anastomotic leak
ASA	American Society of Anesthesiologists
BMI	body mass index
CCI	Comprehensive Complication Index
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease discovered in 2019
CT	computerised tomography
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
FU	follow-up
ICER	incremental cost-effectiveness ratio
ICG-NIR	indocyanine green near infrared
IFA	Intraoperative Fluorescence Angiography
LARS	low anterior resection syndrome
PPI	patient and public involvement
QALY	quality-adjusted life-year
QLQ	Quality of Life Questionnaire
QoL	quality of life
TSC	Trial Steering Committee

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Appendix 1 Summary of protocol amendments

TABLE 1 Summary of protocol amendments

Version and date	Summary of changes
V1.0, dated 7 March 2017	Not applicable (N/A) – original protocol submitted for ethical review
V2.0, dated 18 July 2017	• Updated to allow any near-infrared laparoscopes to be used in the trial • Amendment to secondary-end point wording: 'rate of defunctioning stoma (temporary or permanent)', updated to 'rate of stoma (temporary or permanent)' • Hepatic dysfunction redefined in exclusion criterion 7 • Equivalent serum creatinine levels added to exclusion criterion 8, if eGFR not assessed locally • Updated to allow the first IFA-assessment point to be done extracorporeally or intracorporeally. Wording also loosened for the second IFA assessment ('endoluminal' removed) • Additional FU point included at 12 months post randomisation for UK participants (where this time point fell before the end of the planned FU period, i.e., 90 days following the last participant's operation) • Indemnity section amended in relation to international sites • Minor corrections for example update to key contacts, footnote number corrected
V3.0, dated 28 September 2020	• Increased numbers into microbiome substudy owing to interesting preliminary findings • Removal of Oricol device for microbiome substudy participants • Termination of perfusion substudy • Changes to exclusion criteria: ◦ Exclusion criterion 10. *Use of Oral antibiotics within 8 weeks prior to randomisation*, removed ◦ Added exclusion for immunocompromised patients ◦ Minor correction to exclusion criterion 9 • Updates to rectal microbiome substudy laboratory techniques • Update to concurrent clinical trials guidance • Additional details added in relation to roles and responsibilities (specifically relating to the health economic and microbiome analyses) • Publication policy updated • Wording updated to represent increased number of sites and extended recruitment period • T4 added as an option for T-stage collected at randomisation • Minor typographical corrections • Trial contacts updated
V4.0, dated 12 July 2023	• Interim analysis wording updated • Reduction in overall sample size/recruitment targets • Detail added to document the ceasing of recruitment to the microbiome substudy

EFA, electronic Glomerular Filtration Rate; IFA, Intraoperative Fluorescence Angiography.

Appendix 2 Trial flow diagram

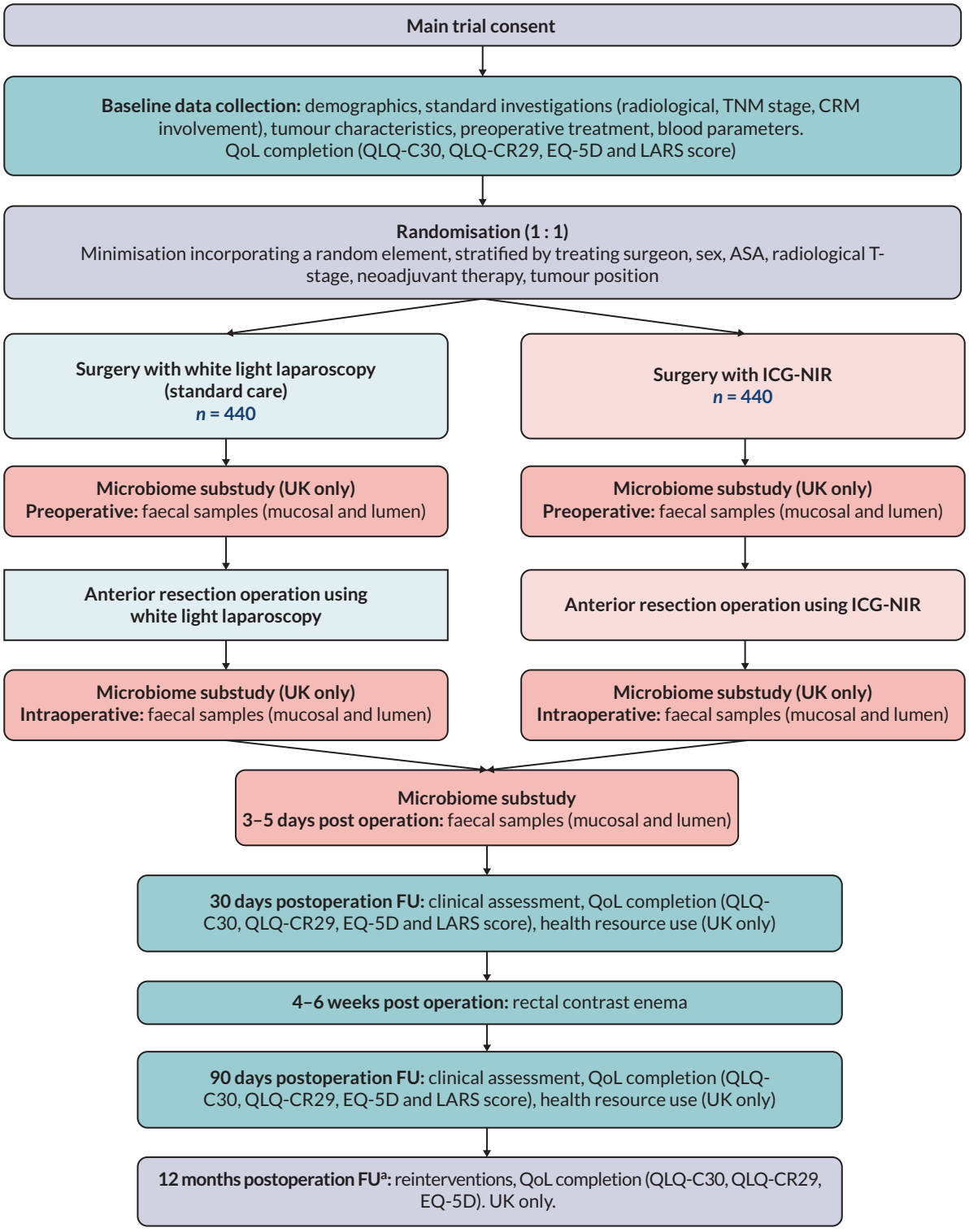

FIGURE 1 Flow diagram. Note that the required sample size was reduced to 766 (383 per arm) after the interim analysis. a If this time point falls within the planned FU period. CRM, Circumferential Resection Margin; TNM, tumour-node-metastasis.

Appendix 3 List of participating centres

TABLE 2 Participating centres

Centre	Country	Date opened to recruitment
St James' University Hospital	UK	20 October 2017
Royal Surrey County Hospital	UK	14 December 2017
Churchill Hospital	UK	18 January 2018
University College London Hospitals	UK	9 February 2018
Derriford Hospital	UK	14 February 2018
Royal Victoria Infirmary	UK	12 March 2018
The Royal London Hospital	UK	13 April 2018
Frimley Park Hospital	UK	22 May 2018
Bradford Royal Infirmary	UK	25 May 2018
Royal Preston Hospital	UK	4 June 2018
University Hospital of Wales	UK	12 June 2018
University Hospital Coventry	UK	10 July 2018
Charité – Universitätsmedizin Berlin	Germany	22 August 2018
St Mark's Hospital	UK	1 October 2018
Royal United Hospital Bath	UK	8 October 2018
York Hospital	UK	12 December 2018
University Medical Centre Ljubljana	Slovenia	31 January 2019
University Hospital Leuven	Belgium	26 February 2019
Amsterdam Medical Center	The Netherlands	15 March 2019
Royal Albert Edward Infirmary	UK	10 October 2019
Morriston Hospital	UK	15 October 2019
The Christie Hospital	UK	13 November 2019
Istituto di Ricovero e Cura e Carattere Scientifico San Raffaele Hospital	Italy	8 January 2020
Istituto Clinico Humanitas	Italy	28 January 2020
Liège University Hospital	Belgium	3 August 2020
Mater Misericordiae University Hospital, Dublin	Ireland	7 October 2020
James Paget Hospital	UK	5 November 2020
Umeå University Hospital	Sweden	14 March 2022

Appendix 4 Summary of the intended operating surgeon at randomisation minimisation factor, by treatment allocation

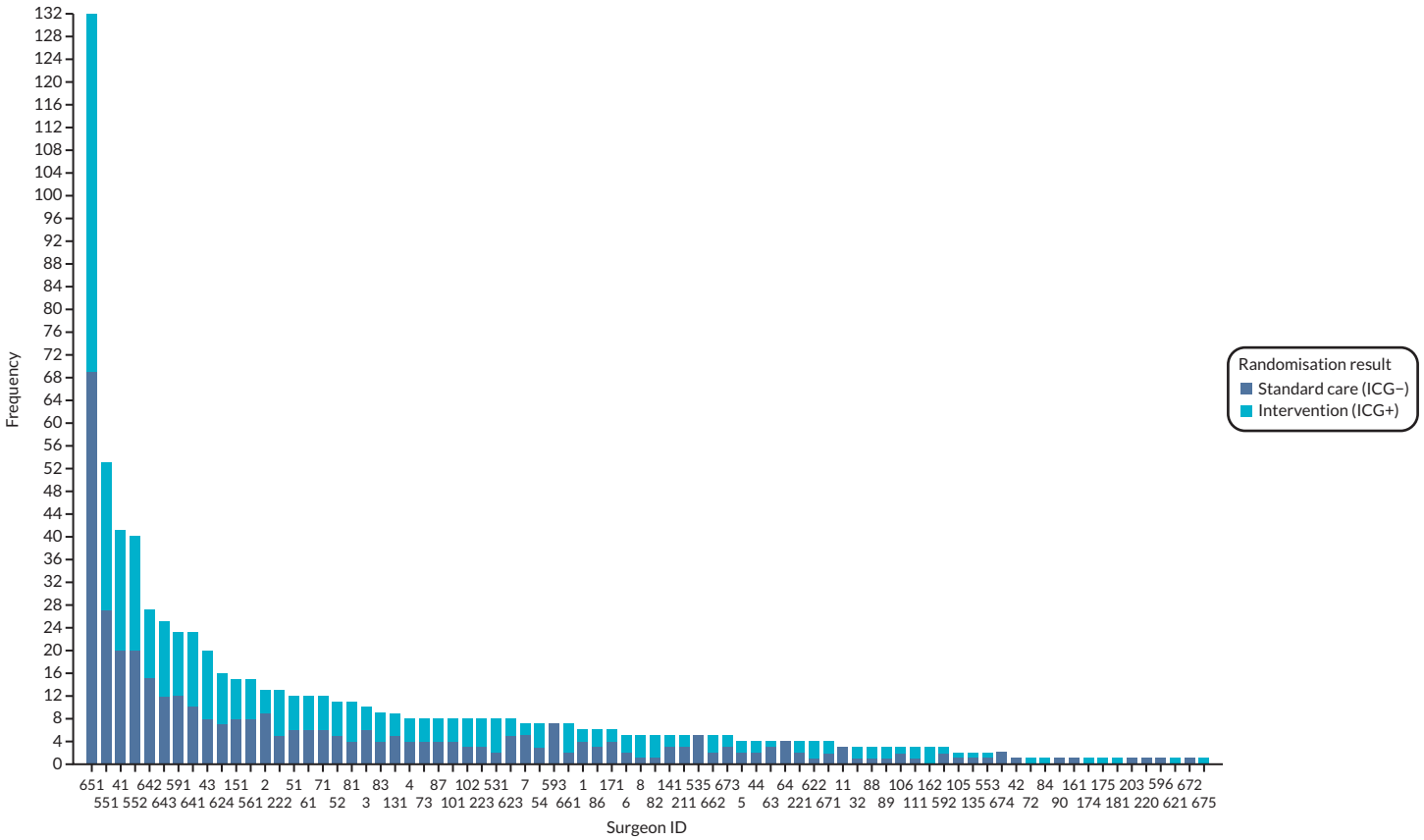

FIGURE 2 Summary of intended operating surgeon.

Appendix 5 Definition and grading of anastomotic leak[4]

TABLE 3 Definition and grading of AL

Definition	Defect of the intestinal wall integrity at the colorectal or colo-anal anastomotic site (including suture and staple lines of neorectal reservoirs) leading to a communication between the intra- and extraluminal compartments. A pelvic abscess close to the anastomosis is also considered as AL.
Grade A	AL requiring no active therapeutic intervention
Grade B	AL requiring active therapeutic intervention but manageable without relaparotomy
Grade C	AL requiring relaparotomy

Appendix 6 Results figures and tables

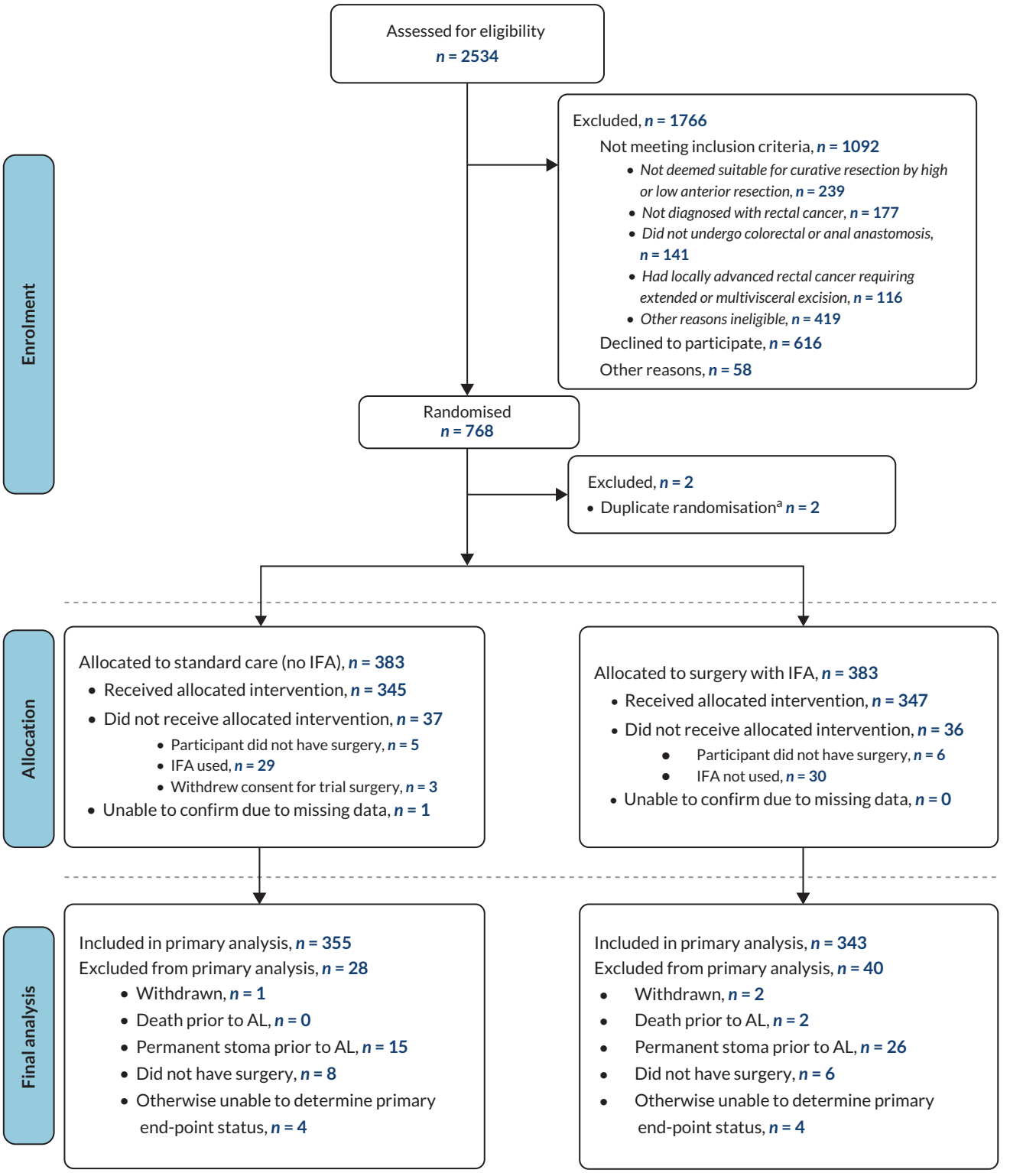

FIGURE 3 Consolidated Standards of Reporting Trials flow diagram. a, Two participants who were mistakenly enrolled twice under different trial numbers; the duplicate participant numbers were removed from the trial. Reproduced from Jayne *et al.*[5] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure above includes minor additions and formatting changes.

TABLE 4 Key baseline characteristics

	Standard care (*n* = 383)	Intervention (ICG-NIR) (*n* = 383)	Total (*n* = 766)
Age (years)			
Mean (SD)	63.3 (11.5)	62.9 (11.6)	63.1 (11.6)
Median (range)	63.5 (22.0–88.0)	64.0 (23.0–89.0)	64.0 (22.0–89.0)
IQR	56.0–72.0	55.0–72.0	56.0–72.0
Missing	1	0	1
Sex[a]			
Male	248 (64.8%)	253 (66.1%)	501 (65.4%)
Female	135 (35.2%)	130 (33.9%)	265 (34.6%)
Neoadjuvant therapy[a]			
None received	217 (56.7%)	214 (55.9%)	431 (56.3%)
Short course with no delay	15 (3.9%)	12 (3.1%)	27 (3.5%)
Short course with delay	16 (4.2%)	20 (5.2%)	36 (4.7%)
Long course	135 (35.2%)	137 (35.8%)	272 (35.5%)
T-stage[a]			
T1	30 (7.8%)	34 (8.9%)	64 (8.4%)
T2	127 (33.2%)	125 (32.6%)	252 (32.9%)
T3	206 (53.8%)	207 (54.0%)	413 (53.9%)
T4	20 (5.2%)	17 (4.4%)	37 (4.8%)
Position of the rectal tumour[a]			
Above peritoneal reflection	119 (31.1%)	116 (30.3%)	235 (30.7%)
At peritoneal reflection	109 (28.5%)	109 (28.5%)	218 (28.5%)
Below peritoneal reflection	155 (40.5%)	158 (41.3%)	313 (40.9%)
ASA grade[a]			
Grade I	75 (19.6%)	72 (18.8%)	147 (19.2%)
Grade II	246 (64.2%)	243 (63.4%)	489 (63.8%)
Grade III	62 (16.2%)	68 (17.8%)	130 (17.0%)
Ethnicity			
White	369 (96.3%)	357 (93.2%)	726 (94.8%)
Mixed – White and Black Caribbean	1 (0.3%)	0 (0.0%)	1 (0.1%)
Other mixed background	0 (0.0%)	1 (0.3%)	1 (0.1%)
Asian – Indian	1 (0.3%)	2 (0.5%)	3 (0.4%)
Asian – Pakistani	0 (0.0%)	1 (0.3%)	1 (0.1%)
Asian – Bangladeshi	0 (0.0%)	1 (0.3%)	1 (0.1%)

TABLE 4 Key baseline characteristics (*continued*)

	Standard care (*n* = 383)	Intervention (ICG-NIR) (*n* = 383)	Total (*n* = 766)
Other Asian background	1 (0.3%)	6 (1.6%)	7 (0.9%)
Black – Caribbean	1 (0.3%)	2 (0.5%)	3 (0.4%)
Black – African	2 (0.5%)	0 (0.0%)	2 (0.3%)
Chinese	0 (0.0%)	1 (0.3%)	1 (0.1%)
Not stated	5 (1.3%)	5 (1.3%)	10 (1.3%)
Other ethnic group	1 (0.3%)	5 (1.3%)	6 (0.8%)
Missing	2 (0.5%)	2 (0.5%)	4 (0.5%)
BMI			
Mean (SD)	26.5 (4.8)	26.7 (4.7)	26.6 (4.7)
Median (range)	26.2 (17.0–48.7)	26.3 (16.6–45.0)	26.2 (16.6–48.7)
IQR	23.1–28.8	23.6–29.3	23.3–29.1
Missing	17	18	35
BMI classification			
Underweight/normal	139 (36.3%)	140 (36.6%)	279 (36.4%)
Overweight	161 (42.0%)	147 (38.4%)	308 (40.2%)
Obese class I	39 (10.2%)	56 (14.6%)	95 (12.4%)
Obese class II	20 (5.2%)	10 (2.6%)	30 (3.9%)
Obese class III	5 (1.3%)	9 (2.3%)	14 (1.8%)
Missing	19 (5.0%)	21 (5.5%)	40 (5.2%)
Smoking status			
Yes, current smoker (within the last month)	49 (12.8%)	45 (11.7%)	94 (12.3%)
No, never smoked	206 (53.8%)	197 (51.4%)	403 (52.6%)
No, ex-smoker	117 (30.5%)	123 (32.1%)	240 (31.3%)
Missing	11 (2.9%)	18 (4.7%)	29 (3.8%)

IQR, interquartile range; SD, standard deviation.
a Minimisation factors at randomisation, alongside intended operating surgeon.

DOI: 10.3310/GJDJ2014

TABLE 5 Main results of the primary and key secondary analyses of AL outcomes

Unadjusted summary of AL grade experienced	**Standard care**	**Intervention (ICG-NIR)**	**Total**
No leak experienced	281 (79.2%)	296 (86.3%)	577 (82.7%)
No active therapeutic intervention (grade A)	20 (5.6%)	11 (3.2%)	31 (4.4%)
Active therapeutic intervention but manageable without relaparotomy (grade B)	31 (8.7%)	11 (3.2%)	42 (6.0%)
Relaparotomy (grade C)	23 (6.5%)	25 (7.3%)	48 (6.9%)
Total	**355 (100%)**	**343 (100%)**	**698 (100%)**
Model estimates: primary analysis model of participants experiencing clinical (grade B/C) ALs only			
Effect	**No. with AL/total no. (%)**	**Adjusted OR (95% CI)**	***p*-value**
Treatment: standard care	54/355 (15.2%)	1 (reference)	N/A
Treatment: surgery with ICG-NIR	36/343 (10.5%)	0.667 (0.419 to 1.060)	0.0868
ASA *grade:* grade I	20/137 (14.6%)	1 (reference)	N/A
ASA *grade:* grade II	53/451 (11.8%)	0.768 (0.427 to 1.380)	0.3714
ASA *grade:* grade III	17/110 (15.5%)	1.081 (0.520 to 2.249)	0.8343
Sex: male	66/455 (14.5%)	1 (reference)	N/A
Sex: female	24/243 (9.9%)	0.617 (0.366 to 1.042)	0.0711
T-stage: T1	6/62 (9.7%)	1 (reference)	
T-stage: T2	33/230 (14.3%)	1.748 (0.672 to 4.546)	0.2518
T-stage: T3	47/376 (12.5%)	1.286 (0.505 to 3.276)	0.5972
T-stage: T4	4/30 (13.3%)	1.731 (0.421 to 7.119)	0.4464
Neoadjuvant therapy: none received	47/397 (11.8%)	1 (reference)	N/A
Neoadjuvant therapy: long-course	29/249 (11.6%)	0.948 (0.551 to 1.629)	0.8454
Neoadjuvant therapy: short-course with delay	7/32 (21.9%)	2.091 (0.809 to 5.407)	0.1278
Neoadjuvant therapy: short-course no delay	7/20 (35.0%)	4.598 (1.641 to 12.882)	0.0038
Tumour position: Below peritoneal reflection	44/287 (15.3%)	1 (reference)	N/A
Tumour position: at peritoneal reflection	28/194 (14.4%)	0.915 (0.533 to 1.569)	0.7459
Tumour position: above peritoneal reflection	18/217 (8.3%)	0.469 (0.254 to 0.864)	0.0153

TABLE 5 Main results of the primary and key secondary analyses of AL outcomes (*continued*)

Unadjusted summary of AL grade experienced	Standard care	Intervention (ICG-NIR)	Total
Random effect variance component estimate from the primary analysis model of participants experiencing clinical (grade B/C) ALs only and ICC			
Effect	**Estimate**	**SE**	**ICC**
Planned surgeon at randomisation (random effect)	0.0609	0.1978	0.0328
Model estimates: key secondary analysis model of participants experiencing all (grade A/B/C) ALs			
Effect	**No. with AL/total no. (%)**	**Adjusted OR (95% CI)**	***p*-value**
Treatment: standard care	74/355 (20.8%)	1 (reference)	N/A
Treatment: surgery with ICG-NIR	47/343 (13.7%)	0.607 (0.403 to 0.915)	0.0172
ASA *grade:* grade I	24/137 (17.5%)	1 (reference)	N/A
ASA *grade:* grade II	77/451 (17.1%)	0.973 (0.573 to 1.652)	0.9178
ASA *grade:* grade III	20/110 (18.2%)	1.055 (0.536 to 2.077)	0.8767
Sex: male	95/455 (20.9%)	1 (reference)	N/A
Sex: female	26/243 (10.7%)	0.443 (0.274 to 0.715)	0.0009
T-stage: T1	7/62 (11.3%)	1 (reference)	N/A
T-stage: T2	46/230 (20.0%)	2.054 (0.859 to 4.910)	0.1052
T-stage: T3	64/376 (17.0%)	1.472 (0.627 to 3.458)	0.3740
T-stage: T4	4/30 (13.3%)	1.472 (0.379 to 5.714)	0.5759
Neoadjuvant therapy: none received	67/397 (16.9%)	1 (reference)	N/A
Neoadjuvant therapy: long-course	39/249 (15.7%)	0.933 (0.563 to 1.547)	0.7882
Neoadjuvant therapy: short-course with delay	8/32 (25.0%)	1.861 (0.766 to 4.523)	0.1701
Neoadjuvant therapy: short-course no delay	7/20 (35.0%)	2.874 (1.053 to 7.842)	0.0394
Tumour position: below peritoneal reflection	56/287 (19.5%)	1 (reference)	N/A
Tumour position: at peritoneal reflection	37/194 (19.1%)	0.954 (0.589 to 1.546)	0.8488
Tumour position: above peritoneal reflection	28/217 (12.9%)	0.580 (0.343 to 0.981)	0.0421
Random effect variance component estimate from the key secondary analysis model of participants experiencing all (grade A/B/C) ALs and ICC			
Effect	**Estimate**	**SE**	**ICC**
Planned surgeon at randomisation (random effect)	0.0046	0.0727	0.0147

ICC, intraclass correlation coefficient; N/A, not applicable.

This synopsis should be referenced as follows: Jayne D, Corrigan N, Croft J, Quirke P, Cahill RA, Ainsworth G, *et al.* Intraoperative Fluorescence Angiography to Prevent Anastomotic Leak in Rectal Cancer Surgery: a synopsis of the IntAct trial. *Efficacy Mech Eval* 2026;**13**(5). https://doi.org/10.3310/GJDJ2014

DOI: 10.3310/GJDJ2014

TABLE 6 Main results from secondary outcome analyses

Binary secondary outcomes		Standard care Numbers with event/total numbers (%)	Surgery with ICG-NIR Numbers with event/total numbers (%)	Adjusted OR (95% CI)	*p*-value
Change in planned anastomosis[a]	Component 1	9/374 (2.4%)	19/377 (5.0%)	2.152 (1.251 to 3.699)	0.0057
	Component 2	11/365 (3.0%)	24/358 (6.7%)		
	Component 3	6/365 (1.6%)	4/358 (1.1%)		
Intraoperative complication (incidence)		16/374 (4.3%)	17/377 (4.5%)	1.113 (0.542 to 2.284)	0.7705
Postoperative complication (incidence)[b]		168/374 (44.9%)	145/377 (38.5%)	0.738 (0.539 to 1.011)	0.0585
Reintervention within 90 days of trial operation		81/374 (21.7%)	66/377 (17.5%)	0.761 (0.523 to 1.107)	0.1529
Death within 90 days of trial operation		2/374 (0.005%)	2/377 (0.005%)	N/A	N/A
Ordinal secondary outcome		**Standard care Numbers with event/total numbers (%)**	**Surgery with ICG-NIR Numbers with event/total numbers (%)**	**Adjusted OR (95% CI)**	***p*-value**
Stoma formation at 90 days post operation	No stoma	132/374 (35.3%)	130/377 (34.5%)	1.163 (0.848 to 1.595)	0.3494
	Defunctioning stoma	216/374 (57.8%)	208/377 (55.2%)		
	Permanent stoma	20/374 (5.3%)	30/377 (8.0%)		
Continuous secondary outcomes		**Standard care**	**Surgery with ICG-NIR**	**Model estimate (95% CI)**	***p*-value**
Postoperative complication (CCI score)[b]	Mean (SD)	27.0 (16.0)	28.3 (17.2)	1.167 (−2.376 to 4.710)	0.5170
	N (Missing)	*163 (5)*	*139 (6)*		
Length of postoperative stay (days)	Mean (SD)	9.7 (9.1)	10.2 (17.9)	0.990 (0.911 to 1.077)	0.8177
	Median (range)	7 (1–110)	7 (1–324)		
	N (Missing)	*373 (10)*	*374 (9)*		

N/A, not applicable; SD, standard deviation.

a Component 1 = Permanent stoma formed instead of an anastomosis, Component 2 = change in proximal transection level, Component 3 = Change in site of rectal stump used for anastomosis.

b See methods for full details of the modelling procedure for postoperative complications. CCI score was only modelled in patients who had at least one postoperative complication.

Notes

Modelling for all end points incorporated a random effect with respect to intended operating surgeon and adjusted for the other minimisation factors as fixed effects.

TABLE 7 Summary data of QoL outcomes

		Standard care	Surgery with ICG-NIR	Total
Global health status				
Baseline	Mean (SD)	73.3 (18.78)	74.2 (18.25)	73.8 (18.51)
	N (missing)	*305 (78)*	*309 (74)*	*614 (152)*
30 days	Mean (SD)	62.6 (20.18)	62.0 (19.77)	62.3 (19.95)
	N (missing)	*186 (197)*	*185 (198)*	*371 (395)*
90 days	Mean (SD)	68.1 (18.36)	65.9 (17.53)	67.0 (17.96)
	N (missing)	*215 (168)*	*220 (163)*	*435 (331)*
12 months	Mean (SD)	72.8 (19.53)	70.5 (21.09)	71.6 (20.32)
	N (missing)	*115 (49)*	*118 (41)*	*233 (90)*
	N/A[a]	*219*	*224*	*443*
LARS total score				
Baseline	Mean (SD)	18.8 (12.45)	20.2 (13.08)	19.5 (12.78)
	N (missing)	*290 (93)*	*288 (95)*	*578 (188)*
30 days	Mean (SD)	26.3 (12.73)	31.4 (10.32)	28.9 (11.76)
	N (missing)	*44 (49)*	*48 (51)*	*92 (100)*
	N/A[b]	*290*	*284*	*574*
90 days	Mean (SD)	28.1 (10.76)	30.0 (10.37)	29.1 (10.57)
	N (missing)	*76 (75)*	*79 (70)*	*155 (145)*
	N/A[b]	*232*	*234*	*466*
EQ-5D utility				
Baseline utility (unadjusted and complete case data)	Mean (SE)	*0.832 (0.015)*	*0.823 (0.013)*	–
	N (missing)	*141 (29)*	*144 (31)*	–
Mean impact of AL (imputed data as base case analysis; *SC vs.* ICG-NIR: *SC* – ICG-NIR)				
90 days	Mean (*p*-value)	*0.084 (0.011)*		–
	CI (lower CI, upper CI)	*0.149 to −0.019*		–
12 months	Mean (*p*-value)	*0.046 (0.297)*		–
	CI (lower CI, upper CI)	*0.134 to −0.041*		–
QALYs[c]				
90 days (complete case)	Mean (SE)	*0.193 (0.0022)*	*0.192 (0.0021)*	–
	N (missing)	*141 (29)*	*144 (31)*	–
90 days (imputed)	Mean (SE)	*0.195 (0.0029)*	*0.193 (0.0026)*	–
	N (missing)	*170 (–)*	*175 (–)*	–
12 months (complete case)	Mean (SE)	*0.765 (0.0152)*	*0.779 (0.0157)*	–
	N (missing)	*100 (70)*	*94 (81)*	–

continued

TABLE 7 Summary data of QoL outcomes (*continued*)

		Standard care	Surgery with ICG-NIR	Total
12 months (imputed)	Mean (SE)	*0.782 (0.010)*	*0.781 (0.011)*	–
	N (missing)	*170 (–)*	*175 (–)*	–

N/A, not applicable; SC, standard care; SD, standard deviation; SE, standard error.
a 12-month time point data were only collected for UK participants whose 12-month time point fell within the overall trial FU period.
b LARS score is not applicable for participants with a stoma, and so is not reported for patients with stomas at the corresponding FU visit.
c QALYs are adjusted by utility at baseline and other relevant covariates.

Appendix 7 Microbiome substudy

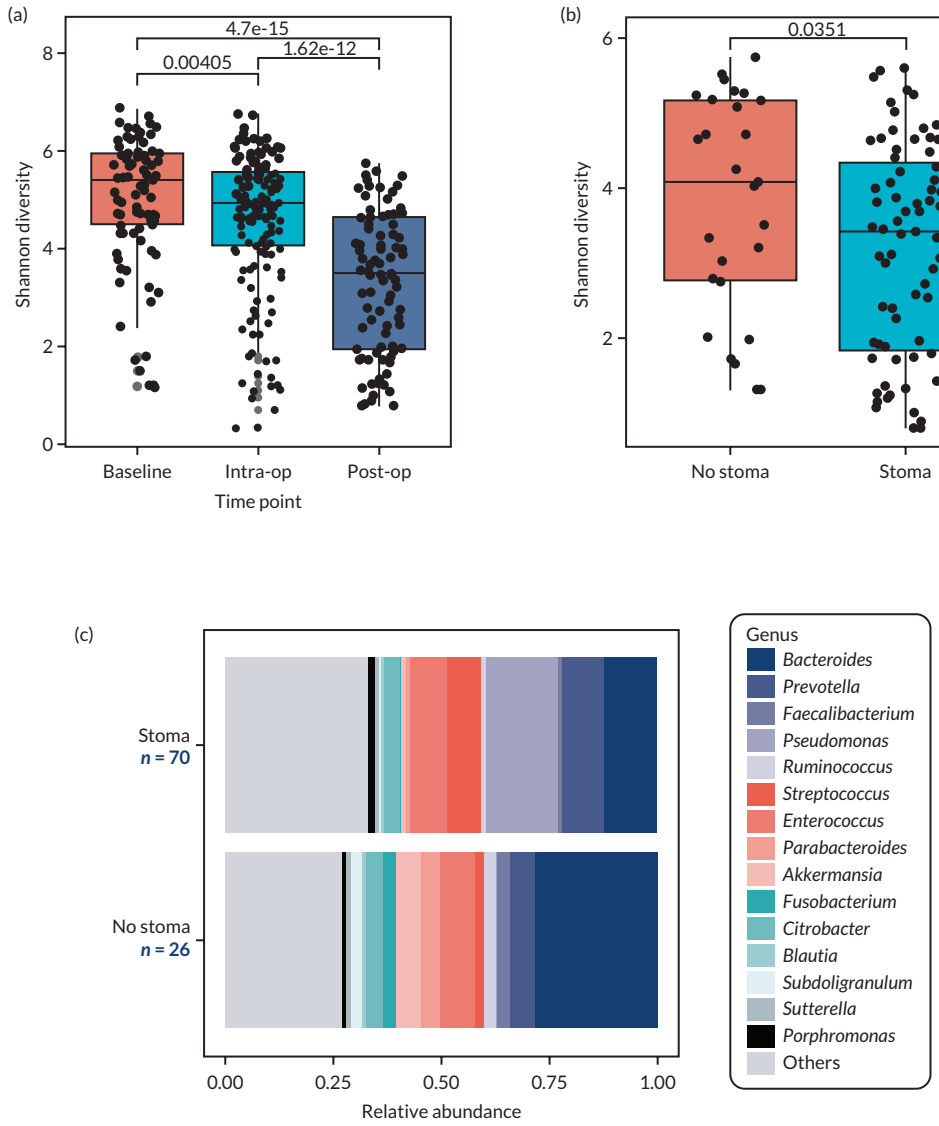

FIGURE 4 Microbiome profiling of the study cohort and impact of defunctioning stoma on postoperative microbiome.

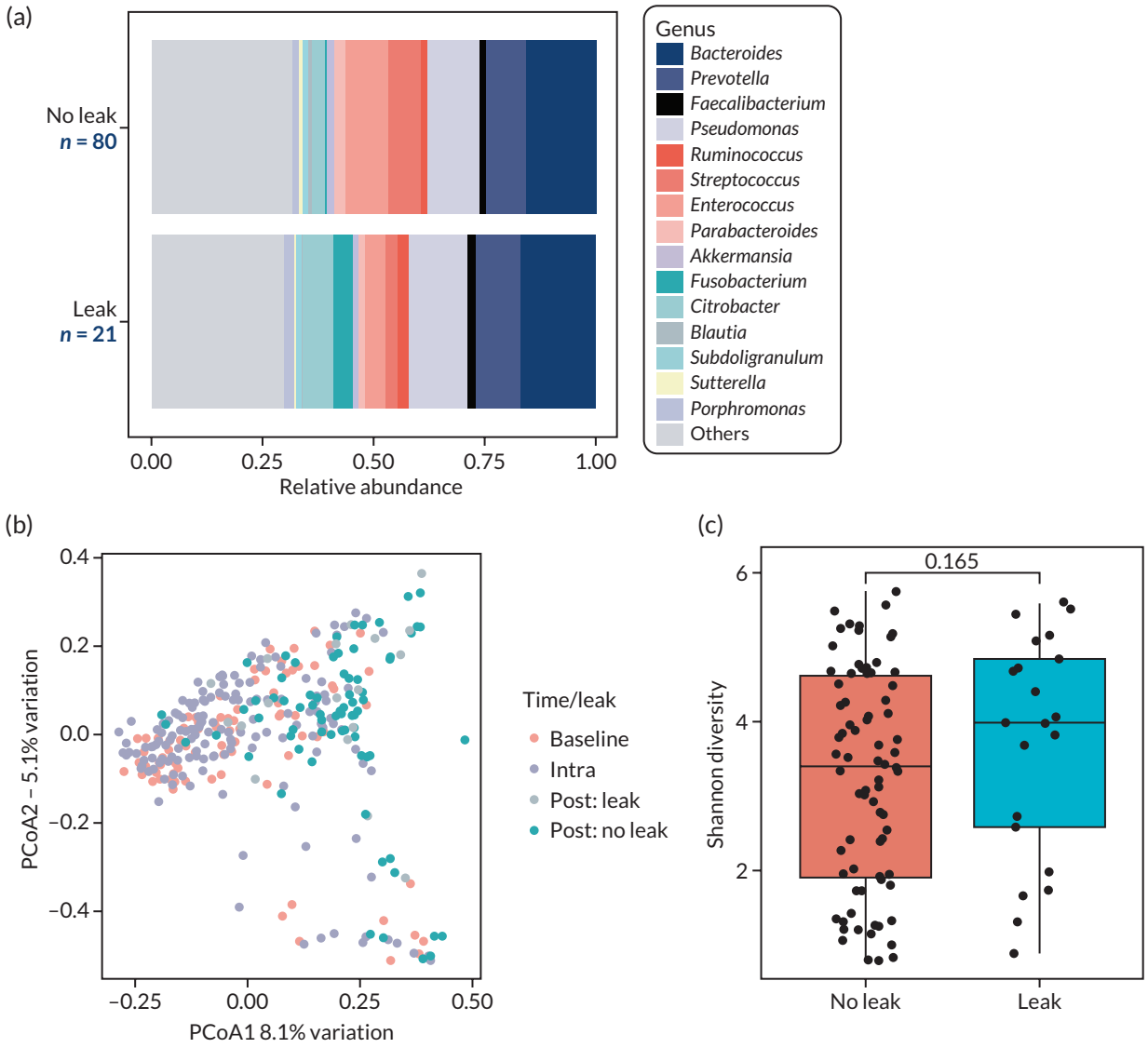

FIGURE 5 Comparison of the postoperative microbiome by AL status.