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# BMJ Open AVOID; a phase III, randomised controlled trial using indocyanine green for the prevention of anastomotic leakage in colorectal surgery

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## ABSTRACT

**Introduction** Anastomotic leakage (AL) is one of the major complications after colorectal surgery. Compromised tissue perfusion at the anastomosis site increases the risk of AL. Several cohort studies have shown that indocyanine green (ICG) combined with fluorescent near-infrared imaging is a feasible and reproducible technique for real-time intraoperative imaging of tissue perfusion, leading to reduced leakage rates after colorectal resection. Unfortunately, these studies were not randomised. Therefore, we propose a randomised controlled trial to assess the value of ICG-guided surgery in reducing AL after colorectal surgery.

**Methods and analysis** A multicentre, randomised controlled clinical trial will be conducted to assess the benefit of ICG-guided surgery in preventing AL. A total of 978 patients scheduled for colorectal surgery will be included. Patients will be randomised between the Fluorescence Guided Bowel Anastomosis group and the Conventional Bowel Anastomosis group. The primary endpoint is clinically relevant AL (defined as requiring active therapeutic intervention or reoperation) within 90 days after surgery. Among the secondary endpoints are 30-day clinically relevant AL, all-cause postoperative complications, all-cause and AL-related mortality, surgical and non-surgical reinterventions, total surgical time, length of hospital stay and all-cause and AL-related readmittance.

**Ethics and dissemination** This protocol has been approved by the Medical Ethical Committee Leiden-Den Haag-Delft (METC-LDD) and is registered at ClinicalTrials.gov and [trialregister.nl](http://trialregister.nl). The results of this study will be reported through peer-reviewed publications and conference presentations.

**Trial registration number** NCT04712032; NL7502.

## INTRODUCTION

Anastomotic leakage (AL) is a major complication after colorectal surgery, accounting for considerable morbidity and mortality.<sup>1–6</sup> The incidence of AL in colorectal surgery ranges from 2.4% to 11% in colon cases and up to 23.3% in rectal cancer surgery.<sup>4–15</sup> The occurrence of AL often has a multifactorial cause,

## Strengths and limitations of this study

- This study is a multicentre randomised controlled trial.
- Anastomotic leakage is a major complication with huge impact on patient's life.
- A clinically relevant endpoint will be used as the primary endpoint.
- Quantification of fluorescence-guided bowel perfusion with indocyanine green would be a preferable addition, however its clinical correlation is unclear at this point.

including risk factors such as tumour location, level of anastomosis, male gender, high American Society of Anesthesiology score, comorbidities, smoking, obesity and (neoadjuvant) radiotherapy.<sup>3 4 6 11 13 14 16</sup>

Most risk factors for AL can no longer be changed at the time of surgery. Therefore, it is important to focus on the few factors that can be influenced, such as compromised tissue perfusion at the anastomosis site. It has been reported that this factor significantly increases the risk of AL.<sup>17–19</sup> Perfusion is commonly assessed by palpating the mesenteric arterial pulsations, inspection of the bowel colour and bleeding at the anastomosis sides. Other intraoperative tests to prove the integrity of the anastomosis are the air leak test and inspection of the resection doughnuts.<sup>20</sup> Though useful, these clinical assessments have proven to have a low predictive value for AL which emphasises the urge for a better diagnostic test.<sup>21</sup>

A promising diagnostic tool is intraoperative near-infrared (NIR) fluorescence imaging. This technique combines a fluorescent contrast agent, for example, indocyanine green (ICG) and a dedicated NIR imaging system.<sup>22</sup> The intravenous injection

of ICG has proven to be a feasible and reproducible application for real-time perfusion assessment.<sup>23–25</sup> ICG was introduced by Fox *et al* in 1957 and is currently used for a variety of diagnostic indications.<sup>26</sup> Diluted and intravenously injected ICG, with a peak emission at 820 nm, is invisible for the naked eye and will therefore not interfere with the surgical field.<sup>27</sup> Moreover, it is cleared quickly by the liver and has low toxicity.<sup>28</sup>

Several cohort studies have investigated the benefit of NIR fluorescence imaging with ICG for intraoperative assessment of bowel perfusion. Some of these studies have shown that this technique enables clear visualisation of bowel perfusion within minutes after intravenous injection of ICG, resulting in reduced leakage rates and hospital stay.<sup>29–32</sup> Moreover, several systematic reviews support this promising results concerning the prevention of AL.<sup>33 34</sup> This has already led to the start of two randomised controlled trials (ICG-COLORAL; NCT03602677 and InTACT trial; ISCRN 13334746) which are currently recruiting patients. On the other hand, Kin *et al* have shown no benefit by using ICG in preventing AL.<sup>35</sup> Major drawbacks of these cohort studies are that they were not randomised and did not use clinically relevant AL as the primary endpoint. Therefore, we propose AVOID: ‘Anastomotic leakage and Value Of Indocyanine green in Decreasing leakage rates’, a randomised controlled trial to investigate the benefit of intraoperative imaging with ICG for the reduction of AL rate in colorectal surgery.

## METHODS AND ANALYSIS

### Primary aim

The main objective of this study is to assess if ICG-guided perfusion assessment will result in a reduction of the AL rate within 90 days after surgery. ICG-guided perfusion assessment will be an adjunct to conventional laparoscopic imaging versus conventional laparoscopic imaging alone.

### Hypothesis

It is hypothesised that intraoperative assessment of bowel perfusion using NIR fluorescence imaging with ICG will lower the incidence of clinically relevant AL within 90 days after colorectal resection.

### Study design

In this multicentre randomised controlled trial, patients will be allocated to two groups: the Fluorescence Guided Bowel Anastomosis group (FGBA) or the Conventional Bowel Anastomosis (CBA) group. Patients in the FGBA group will receive at least one dose of 5 mg ICG, up to a maximum of three doses, to assess bowel perfusion. Patients in the CBA group will not receive any study-related interventions and will be treated according to standard of care. The allocated treatment result is not blinded for the surgeon performing the procedure. Patients will be unblinded after the procedure.

### Setting

This national study will take place in multiple academic and large teaching hospitals in the Netherlands. More Dutch hospitals will be added during the course of the study.

### Participants

All patients scheduled for laparoscopic or robotic-assisted colorectal surgery (malignant and benign indications) with primary anastomosis will be screened for eligibility during multidisciplinary team meetings and, when eligible for participation, informed about the study by their attending physician. It will be emphasised that a patient can withdraw from the study at any given moment without having to offer any reason. The fundamental concepts outlined in the Declaration of Helsinki will be followed during the execution of the trial.<sup>36</sup>

### Sample size calculation

The power analysis was performed based on Dutch national AL percentages, derived from the Dutch ColoRectal Audit.<sup>37</sup> It is hypothesised that the use of ICG will decrease the AL rate in colorectal surgery from 7% to 3%. With a significance of 0.0492 (adjusted for the interim analysis using the O’Brien-Flemming approach), power of 80%, drop-out of 5% and a control-intervention ratio of 1:1, a sample size of 978 (489:489) patients is needed.<sup>38</sup>

### Inclusion criteria

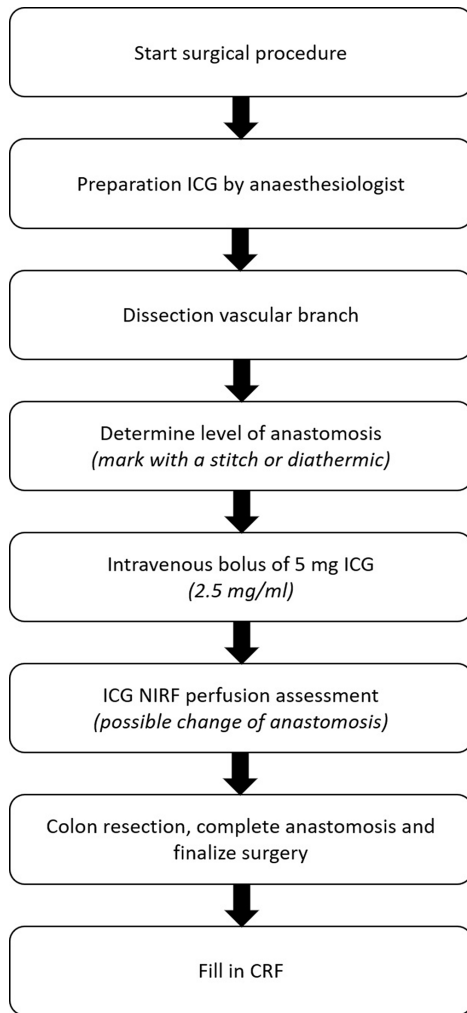
In order to be eligible to participate in this study, a patient must meet all of the following criteria: aged 18 years and above, scheduled for laparoscopic or robotic-assisted colorectal resection with primary anastomosis, able to communicate in the Dutch language and willing to comply with the study restrictions and signed informed consent prior to any study-mandated procedure.

### Exclusion criteria

A potential patient who meets any of the following criteria will be excluded from participation in this study: known allergy or history of adverse reaction to ICG, iodine or iodine dyes, severe liver or kidney insufficiency, hyperthyroidism or a benign thyroid tumour, pregnant or breastfeeding women, scheduled for emergency surgery, palliative surgery or terminally ill, scheduled for a defunctioning stoma, taking phenobarbital, phenylbutazone, primidone, phenytoin, haloperidol, nitrofurantoin and probenecid or any other condition that the investigator considers to be potentially jeopardising the patients well-being or the study objectives (following a detailed medical history and physical examination).

### Randomisation

After inclusion in the study (ie, after written informed consent is obtained), patients will be randomised to the FGBA or the CBA group. Randomisation will be performed online via Castor EDC (Castor, Amsterdam, the Netherlands) with variable block sizes and stratified



**Figure 1** Surgical flowchart. CRF, case report form; ICG, indocyanine green; NIRF, near-infrared fluorescence.

by institute. The allocated treatment result is not blinded for the surgeon performing the procedure. Patients will be unblinded after the surgical procedure.

### Intervention

Patients in the CBA group will undergo laparoscopic or robotic colorectal resection according to standard of care using conventional methods to assess the integrity and viability of the anastomosis. Patients in the FGBA group will undergo the same standard of care surgical procedure as patients in the CBA group; however, in addition to the conventional methods, NIR fluorescence imaging with ICG will be performed to assess the bowel perfusion at the anastomosis side. All surgeries, in both arms, will be performed by an attending surgeon. NIR fluorescence imaging with ICG will be performed as follows (figure 1): after dissection of the vascular branch, the preferred level of anastomoses (proximally and distally) will be highlighted by a stitch or diathermic mark in the adjacent mesocolon or mesorectum. Then, 5 mg ICG (2.5 mg/mL, Diagnostic Green, Aschheim, Germany), followed by 10 mL saline flush, will be injected intravenously by the anaesthesiologist. Within a few minutes, the anastomotic

microvascularisation of both bowel ends will be assessed using the Olympus Medical Imaging Video System and Laparoscope (Olympus, Leiderdorp, the Netherlands) or Da Vinci Firefly (Intuitive, Sunnyvale, CA, USA). The green overlay setting of these systems will be used for perfusion assessment. The level of resection and subsequent anastomosis may be changed accordingly (with the mesocolic stitch serving as the baseline). During the procedure, the ICG injection (5 mg) may be repeated for a second or third time with a 15-min wash-out period between each administration. Repeated doses may be applicable when, for example, both anastomosis sides do not fit into the optical field, or when perfusion seems compromised after anastomosis finalisation. All injections, including the reason(s) for repeated injection(s), and the consequences of administration, will be documented in the case report form (CRF).

The 90-day follow-up is a standard of care follow-up moment in all participating hospitals. It will be done either by phone, by videoconference or in person, according to standard of care in the participating hospital. Patients who, for any reason, do not visit the hospital 90 days after resection, will be contacted by phone and asked for any postoperative complications or reinterventions.

### Outcome measures

#### Primary outcome

The primary outcome is the rate of clinically relevant AL within 90 days after surgery. This will be compared between the FGBA group using ICG for perfusion assessment and the standard of care surgery, CBA group. The definition of clinically relevant AL is derived from the definition of Rahbari *et al.*<sup>39</sup> Grades B (requiring active therapeutic intervention but manageable without reoperation) and C AL (requiring reoperation) will be considered clinically relevant. There is no central study protocol for the detection of AL. No routine CT scans will be performed for AL assessment. Postoperative blood tests, radiologic assessment and subsequent assessment of AL will be based on local protocols and the judgement of the local surgical team.

#### Secondary outcomes

1. 30-day clinically relevant AL
2. 30-day and 90-day all-cause postoperative complications
3. 30-day and 90-day mortality; all-cause and AL related.
4. 30-day and 90-day reinterventions; surgical and non-surgical
5. Total surgical time of primary surgery
6. Postoperative length of hospital stay; primary stay and readmittance within 90 days
7. Readmittance; all-cause and AL related

#### Training

Prior to their first inclusion, surgeons and other involved hospital staff of the participating centre will be trained during a site initiation visit by the principal investigator or

one of the coordinating investigators. If needed, training with the Olympus Medical Imaging Video System and Laparoscope or Da Vinci Firefly will be provided by either Olympus or Intuitive. Surgeons are invited to observe surgical procedures, using NIR fluorescence imaging with ICG for intraoperative assessment of bowel perfusion, in the Leiden University Medical Centre (LUMC). One of the coordinating investigators, with a broad experience in fluorescence-guided surgery, will assist all participating surgeons during their first number of cases to ensure standardisation of the technique.

This study is performed in collaboration with Olympus. In order to keep the study data as homogeneous as possible, the use of camera system has been limited to the Olympus Medical Imaging Video System and the Da Vinci Firefly in case of robotic-assisted surgery.

### Data collection

A CRF will be filled in during surgery by trained local research staff. This CRF captures baseline characteristics, basic surgical data and study specific data. For patients in the FGBA group, it will be documented whether the resection margins have been adjusted and, if so, which margin (distal or proximal margin) and the extent of adjustment in centimetres. In addition, in case of a non-planned defunctioning stoma, it will be recorded whether ICG-guidance contributed to this decision. All clinical data will be prospectively registered via an electronic CRF (eCRF) in a digital database of Castor EDC. We will not transfer or collect imaging data (video or pictures) for postoperative analysis.

### Data validation and management

Patient data will be registered coded and analysed by comparing the FGBA group with the CBA group. Only the local investigators will have access to local source data after informed consent is given. The research group from LUMC will have access to all coded data in the Castor EDC database.

### Study timeline

Patients have been included in the study from July 2020, starting in the LUMC. As per 1 August 2021, 352 patients were included in six different hospitals. With a mean inclusion rate of 40 patients per month, the anticipated last inclusion will be in the final quarter of 2022. There is no maximum for the number of centres nor the number of inclusions per centre.

### Statistical analysis

The most recent version of SPSS (IBM, Armonk, New York, USA) will be used for statistical analysis. Categorical variables of the FGBA and CBA group will be compared by the  $\chi^2$  test. Numerical variables will be compared by the independent sample t-test or the Mann-Whitney U test, depending on distribution. All p-values will be two-sided. A p-value of less than 0.0492 will indicate a statistically significant difference. All data will be analysed on

an intention-to-treat principle and, when applicable, on a per protocol analysis.

The primary outcome measure, clinically relevant AL within 90 days after surgery, will be compared using the Mantel-Haenszel test, stratified by centre.

An interim analysis will be conducted after 489 patients have been randomised and reached the last day of follow-up (day 90). This interim analysis will aim at stopping the study for futility, if the conditional power for the primary endpoint (clinically relevant AL within 90 days after surgery) with the planned sample size, based on the observed results at the interim analysis, using the original settings of null and alternative hypothesis, is less than 10%.

If this interim analysis shows efficacy based on the primary endpoint with a nominal alpha level of 0.0054, the study will be stopped as well. Already included patients will be followed until the last follow-up moment.

Subgroup analysis will be conducted by separately assessing patients with (1) colon and rectal resections, (2) left-sided and right-sided resections, (3) malignant and benign pathology and (4) laparoscopic and robotic-assisted surgery.

### Data monitoring

The study will be monitored for quality and regulatory compliance, by study-independent LUMC staff. Monitoring frequency will be at least annually, but may be increased depending on findings.

### Adverse events

All adverse events related to ICG will be reported. Furthermore, all events that are serious adverse events will be registered in the online Dutch database, toetsingonline.nl and in the eCRF of Castor EDC.

### Patient and public involvement

Patients or public were neither involved in the development of the research questions and outcome measures nor the planning of the study design. Patients are not involved in the recruitment or conduct of the study. Results of the study will be published in peer-reviewed journals, no other information of the results of the study are provided to the patients. Patients will not take part in assessment regarding possible burden of the interventions of this study.

### EXPECTED LIMITATIONS AND DIFFICULTIES

Intraoperative fluorescence assessment of bowel perfusion is currently a subjective tool. This will most likely influence our results as over 30 different surgeons will interpret the fluorescence output. Quantification of the NIR fluorescence signal would improve standardised assessment of tissue perfusion.

Using different NIR platforms (the Olympus Medical Imaging Video System and Laparoscope, and the Da Vinci Firefly) will have some influence on our results as well. Nevertheless, both systems are optimised for the

detection of ICG, we therefore think its effect on our study results is minimal.

AL after colorectal surgery is a multifactorial complication. It is unclear which percentage of AL is solely based on compromised perfusion. It is especially questionable if compromised perfusion plays a role in late AL (>7 days after surgery).

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**Contributors** RPJM, RAF, ODB, JPBMB, EM-KK, JSJM, KB, ALV and DEH all contributed to the study concept and design. HP was responsible for the statistical analysis plan and the sample size calculation. RPJM, RAF and ODB prepared the manuscript. JPBMB, ALV and DEH supervised the manuscript preparation. All authors and members of the AVOID study group reviewed the manuscript before submission.

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**Competing interests** ALV and LS are members of the Diagnostic Green advisory board. All other authors declare to have no competing interest concerning this work.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

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#### REFERENCES

- Buchs NC, Gervaz P, Secic M, *et al*. Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. *Int J Colorectal Dis* 2008;23:265–70.
- Chambers WM, Mortensen NJM. Postoperative leakage and abscess formation after colorectal surgery. *Best Pract Res Clin Gastroenterol* 2004;18:865–80.
- Bakker IS, Grossmann I, Henneman D, *et al*. Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit. *Br J Surg* 2014;101:424–32.
- Walker KG, Bell SW, Rickard MJFX, *et al*. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. *Ann Surg* 2004;240:255–9.
- Isbister WH. Anastomotic leak in colorectal surgery: a single surgeon's experience. *ANZ J Surg* 2001;71:516–20.
- Kang CY, Halabi WJ, Chaudhry OO, *et al*. Risk factors for anastomotic leakage after anterior resection for rectal cancer. *JAMA Surg* 2013;148:65–71.
- Platell C, Barwood N, Dorfmann G, *et al*. The incidence of anastomotic leaks in patients undergoing colorectal surgery. *Colorectal Dis* 2007;9:71–9.
- Vignali A, Fazio VW, Lavery IC, *et al*. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. *J Am Coll Surg* 1997;185:105–13.
- Single-stage treatment for malignant left-sided colonic obstruction: a prospective randomized clinical trial comparing subtotal colectomy with segmental resection following intraoperative irrigation. The SCOTIA Study Group. Subtotal Colectomy versus On-table Irrigation and Anastomosis. *Br J Surg* 1995;82:1622–7.
- Köckerling F, Rose J, Schneider C, *et al*. Laparoscopic colorectal anastomosis: risk of postoperative leakage. Results of a multicenter study. Laparoscopic Colorectal Surgery Study Group (LCSSG). *Surg Endosc* 1999;13:639–44.
- Frasson M, Flor-Lorente B, Rodríguez JLR, *et al*. Risk factors for anastomotic leak after colon resection for cancer: multivariate analysis and nomogram from a multicentric, prospective, national study with 3193 patients. *Ann Surg* 2015;262:321–30.
- Senagore A, Lane FR, Lee E, *et al*. Bioabsorbable staple line reinforcement in restorative proctectomy and anterior resection: a randomized study. *Dis Colon Rectum* 2014;57:324–30.
- Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. *Ann Surg* 2004;240:260–8.
- Yeh CY, Changchien CR, Wang J-Y, *et al*. Pelvic drainage and other risk factors for leakage after elective anterior resection in rectal cancer patients: a prospective study of 978 patients. *Ann Surg* 2005;241:9–13.
- Hyman N, Manchester TL, Osler T, *et al*. Anastomotic leaks after intestinal anastomosis: it's later than you think. *Ann Surg* 2007;245:254–8.
- Snijders HS, Henneman D, van Leersum NL, *et al*. Anastomotic leakage as an outcome measure for quality of colorectal cancer surgery. *BMJ Qual Saf* 2013;22:759–67.
- Vignali A, Gianotti L, Braga M, *et al*. Altered microperfusion at the rectal stump is predictive for rectal anastomotic leak. *Dis Colon Rectum* 2000;43:76–82.
- Kologlu M, Yorganci K, Renda N, *et al*. Effect of local and remote ischemia-reperfusion injury on healing of colonic anastomoses. *Surgery* 2000;128:99–104.
- Sheridan WG, Lowndes RH, Young HL. Tissue oxygen tension as a predictor of colonic anastomotic healing. *Dis Colon Rectum* 1987;30:867–71.
- Hirst NA, Tierman JP, Millner PA, *et al*. Systematic review of methods to predict and detect anastomotic leakage in colorectal surgery. *Colorectal Dis* 2014;16:95–109.
- Karliczek A, Harlaar NJ, Zeebregts CJ, *et al*. Surgeons lack predictive accuracy for anastomotic leakage in gastrointestinal surgery. *Int J Colorectal Dis* 2009;24:569–76.
- van Manen L, Handgraaf HJM, Diana M, *et al*. A practical guide for the use of indocyanine green and methylene blue in fluorescence-guided abdominal surgery. *J Surg Oncol* 2018;118:283–300.
- Jafari MD, Wexner SD, Martz JE, *et al*. Perfusion assessment in laparoscopic left-sided/anterior resection (Pillar II): a multi-institutional study. *J Am Coll Surg* 2015;220:82–92.
- van den Hoven P, Ooms S, van Manen L, *et al*. A systematic review of the use of near-infrared fluorescence imaging in patients with peripheral artery disease. *J Vasc Surg* 2019;70:286–97.
- Griffiths M, Chae MP, Rozen WM. Indocyanine green-based fluorescent angiography in breast reconstruction. *Gland Surg* 2016;5:133–49.
- Fox IJ, Brooker LG, Heseltine DW, *et al*. A tricarboyanine dye for continuous recording of dilution curves in whole blood independent of variations in blood oxygen saturation. *Proc Staff Meet Mayo Clin* 1957;32:478–84.
- Sauda K, Imasaka T, Ishibashi N. Determination of protein in human serum by high-performance liquid chromatography with semiconductor laser fluorometric detection. *Anal Chem* 1986;58:2649–53.
- Landsman ML, Kwang G, Mook GA, *et al*. Light-absorbing properties, stability, and spectral stabilization of indocyanine green. *J Appl Physiol* 1976;40:575–83.



- 29 Kudzus S, Roesel C, Schachtrupp A, *et al.* Intraoperative laser fluorescence angiography in colorectal surgery: a noninvasive analysis to reduce the rate of anastomotic leakage. *Langenbecks Arch Surg* 2010;395:1025–30.
- 30 Boni L, Fingerhut A, Marzorati A, *et al.* Indocyanine green fluorescence angiography during laparoscopic low anterior resection: results of a case-matched study. *Surg Endosc* 2017;31:1836–40.
- 31 Kim JC, Lee JL, Yoon YS, *et al.* Utility of indocyanine-green fluorescent imaging during robot-assisted sphincter-saving surgery on rectal cancer patients. *Int J Med Robot* 2016;12:710–7.
- 32 Jafari MD, Lee KH, Halabi WJ, *et al.* The use of indocyanine green fluorescence to assess anastomotic perfusion during robotic assisted laparoscopic rectal surgery. *Surg Endosc* 2013;27:3003–8.
- 33 Song M, Liu J, Xia D, *et al.* Assessment of intraoperative use of indocyanine green fluorescence imaging on the incidence of anastomotic leakage after rectal cancer surgery: a PRISMA-compliant systematic review and meta-analysis. *Tech Coloproctol* 2021;25:49–58.
- 34 Chan DKH, Lee SKF, Ang JJ. Indocyanine green fluorescence angiography decreases the risk of colorectal anastomotic leakage: systematic review and meta-analysis. *Surgery* 2020;168:1128–37.
- 35 Kin C, Vo H, Welton L, *et al.* Equivocal effect of intraoperative fluorescence angiography on colorectal anastomotic leaks. *Dis Colon Rectum* 2015;58:582–7.
- 36 World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191–4.
- 37 Dupont WD, Plummer WD. Power and sample size calculations. A review and computer program. *Control Clin Trials* 1990;11:116–28. doi:10.1016/0197-2456(90)90005-m
- 38 O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549–56.
- 39 Rahbari NN, Weitz J, Hohenberger W, *et al.* Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery* 2010;147:339–51.