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AVOID; a Phase III, Randomised Controlled Trial Using Indocyanine Green for the Prevention of Anastomotic Leakage in Colorectal Surgery

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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 (FGBA) group and the Conventional Bowel Anastomosis (CBA) group. The primary endpoint is clinically relevant AL (defined as requiring active therapeutic intervention or re-operation) 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. The results of this study will be reported through peer-reviewed publications and conference presentations.

Trial registration numbers: NCT04712032

Keywords: bowel perfusion, near infrared fluorescence, indocyanine green, colorectal surgery, colorectal cancer, inflammatory bowel disease

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Article Summary

Strengths and limitations of this study

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

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Introduction

Anastomotic leakage (AL) is a major complication after colorectal surgery, accounting for considerable morbidity and mortality.[1-6] 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.[4-15] The occurrence of AL often has a multifactorial cause, including risk factors such as tumour location, level of anastomosis, male gender, high ASA score, comorbidities, smoking, obesity and (neoadjuvant) radiotherapy.[3 4 6 11 13 14 16]

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.[17-19] 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.[20] Though useful, these clinical assessments have proven to have a low predictive value for AL which emphasises the urge for a better diagnostic test.[21]

A promising diagnostic tool is intraoperative near-infrared (NIR) fluorescence imaging. This technique combines a fluorescent contrast agent, e.g. indocyanine green (ICG), and a dedicated NIR imaging system.[22] The intravenous injection of ICG has proven to be a feasible and reproducible application for real-time perfusion assessment.[23-25] ICG was introduced by Fox et al. in 1957 and is currently used for a variety of diagnostic indications.[26] Diluted and intravenously injected ICG, with a peak emission at 820 nm, is

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3invisible for the naked eye and will therefore not interfere with the surgical field.[27]
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5Moreover, it is cleared quickly by the liver and has low toxicity.[28]
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9Several cohort studies have investigated the benefit of NIR fluorescence imaging with ICG for
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11intraoperative assessment of bowel perfusion. Some of these studies have shown that this
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13technique enables clear visualisation of bowel perfusion within minutes after intravenous
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15injection of ICG, resulting in reduced leakage rates and hospital stay.[29-32] Moreover,
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17several systematic reviews support this promising results concerning the prevention of AL. On
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19the other hand, Kin et al. have shown no benefit by using ICG in preventing AL.[33] Major
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21drawbacks of these studies are that they were not randomised and did not use clinically
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23relevant AL as the primary endpoint. Therefore, we propose AVOID: '*Anastomotic leakage*
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25*and Value Of Indocyanine green in Decreasing leakage rates*', a randomised controlled trial
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27to investigate the benefit of intraoperative imaging with ICG for the reduction of AL rate in
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29colorectal surgery.
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METHODS AND ANALYSIS

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Primary aim

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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.

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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 group (CBA). Patients in the FGBA group will receive at least one dose of 5 milligram ICG, up to a maximum of 3 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 study will take place in at least two academic hospitals and multiple large teaching hospitals in the Netherlands. More centres 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 emphasized 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.[34]

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Sample size calculation

The power analysis was performed based on Dutch national AL percentages, derived from the Dutch ColoRectal Audit (DCRA).[35] It is hypothesized 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.[36]

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 jeopardizing the patients well-being or the study objectives (following a detailed medical history and physical examination).

Randomisation

After inclusion in the study (i.e., 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 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. This technique 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 Inc., Sunnyvale, CA, United States of America). 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 minute wash-out period between each

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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), time of administration and consequences of administration, will be documented in the case report form (CRF).

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.[37] Grade B (requiring active therapeutic intervention but manageable without re-operation) and C AL (requiring re-operation) will be considered clinically relevant.

Secondary outcomes

- 1. 30-day clinically relevant AL
- 2. 30- and 90-day all-cause postoperative complications
- 3. 30- and 90-day mortality; all-cause and AL related
- 4. 30- 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

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.

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 Leiden University Medical Centre (LUMC) will have access to all coded data in the Castor EDC database.

Study timeline

Patients will be included in the study from July 2020, starting in the LUMC, and with an anticipated last inclusion in the final quarter of 2022. In addition, it is expected that patients can be enrolled in at least 7 additional hospitals in the first year. There is no maximum for the number of centres or 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-Square 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 2-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.

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 indocyanine green 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.

ETHICS AND DISSEMINATION

The study was approved by the certified Medical Ethics Review Committee Leiden, Den Haag, Delft (METC-LDD) on 11 November 2019 under identifier P19.079, and feasibility declarations as required by Dutch law, were obtained for the remaining hospitals. The protocol's current version (2.0) is dated 26 March 2020. The first patient was recruited on 2 July 2020 in LUMC. Six centres are currently enrolling patients. Protocol amendments will first be reviewed by the METC-LDD and after approval be shared with the participating centres for local feasibility declarations.

A manuscript with the results of this study will be published in a peer-reviewed journal. Moreover, the results will be shared via conference presentations.

AUTHOR CONTRIBUTIONS

RM, RF, OB, JB, EM, JB, DH and AV all contributed to the study concept and design. HP was responsible for the statistical analysis plan and the sample size calculation. RM, RF and OB prepared the manuscript. DH and AV supervised the manuscript preparation. All authors and members of the AVOID study group reviewed the manuscript before submission.

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COMPETING INTERESTS STATEMENT

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

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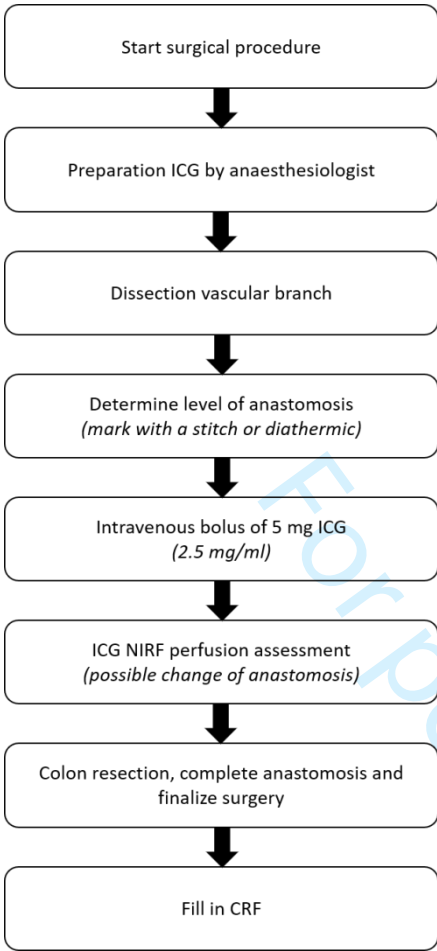


Figure 1 Surgical flowchart

ICG indocyanine green, NIRF Near-infrared, CRF case report form

Appendix A: List of members of the AVOID study group

Academic committee

Ruben P.J. Meijer, Robin A. Faber, Okker D. Bijlstra, Jeffrey P.B.M. Braak, E. Meershoek-Klein
Kranenbarg, Hein Putter, Jacobus Burggraaf, Alexander L. Vahrmeijer, Denise E. Hilling

Participating investigators (in alphabetical order)

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A.M. Brouwers (HAGA hospital, The Hague, The Netherlands), Esther C.J. Consten (Meander
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Capelle aan den IJssel, The Netherlands), Dashti Faraj (Groene Hart Hospital, Gouda, The
Netherlands), Paul D. Gobardhan (Amphia Hospital, The Netherlands), Fabian .A. Holman
(Leiden University Medical Center, Leiden, The Netherlands), Tessa Kauwenbergh (IJsselland
Hospital, Capelle aan den IJssel, The Netherlands), Andreas W.K.S. Marinelli (Haaglanden
Medical Center, The Hague, The Netherlands), Peter A. Neijenhuis (Alrijne Hospital,
Leiderdorp, The Netherlands), Koen C.M.J. Peeters (Leiden University Medical Center,
Leiden, The Netherlands), Daan J. Sikkenk (Meander Medical Center, Amersfoort, The
Netherlands), Laurents P.S. Stassen (Maastricht University Medical Center, Maastricht, The
Netherlands), Willem-Hans Steup (HAGA hospital, The Hague, The Netherlands), Maxime
J.M. van der Valk (IJsselland Hospital, Capelle aan den IJssel, The Netherlands), Bob J. van

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Wely (Bernhoven, Uden, The Netherlands), Lissa Wullaert (Amphia Hospital, The Netherlands)

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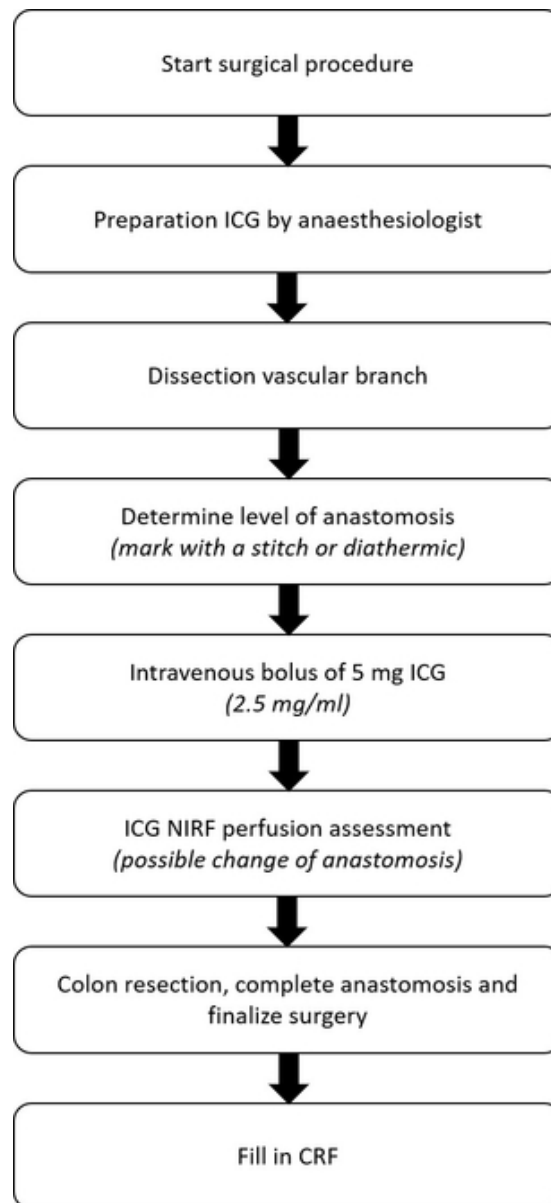


Figure 1 Surgical flowchart
ICG indocyanine green, NIRF Near-infrared, CRF case report form
12x28mm (600 x 600 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

Reporting Item		Page Number
Administrative information		
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	#2a	Trial identifier and registry name. If not yet

		registered, name of intended registry	
Trial registration:	#2b	All items from the World Health Organization	5-11
data set		Trial Registration Data Set	
Protocol version	#3	Date and version identifier	12
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or	10-11

1			groups overseeing the trial, if applicable (see	
2			Item 21a for data monitoring committee)	
3				
4				
5				
6	Introduction			
7				
8				
9	Background and	#6a	Description of research question and justification	4-5
10				
11	rationale		for undertaking the trial, including summary of	
12			relevant studies (published and unpublished)	
13			examining benefits and harms for each	
14			intervention	
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21	Background and	#6b	Explanation for choice of comparators	5-6
22				
23	rationale: choice of			
24				
25	comparators			
26				
27				
28	Objectives	#7	Specific objectives or hypotheses	5
29				
30				
31				
32	Trial design	#8	Description of trial design including type of trial	5-11
33			(eg, parallel group, crossover, factorial, single	
34			group), allocation ratio, and framework (eg,	
35			superiority, equivalence, non-inferiority,	
36			exploratory)	
37				
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39				
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44	Methods:			
45				
46	Participants,			
47				
48	interventions, and			
49				
50	outcomes			
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53				
54	Study setting	#9	Description of study settings (eg, community	6
55			clinic, academic hospital) and list of countries	
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		where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a, patients can withdraw, but intervention will not be modified. Doses can not be changed.
Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a there is only 1 intervention (during surgery) that a patient has to adhere to.
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8-9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg,	9

		predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
concealment mechanism			
Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
implementation			
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a surgeons are always unblinded
emergency unblinding			
Methods: Data collection, management, and analysis			

1	Data collection plan	#18a	Plans for assessment and collection of outcome,	10
2			baseline, and other trial data, including any	
3			related processes to promote data quality (eg,	
4			duplicate measurements, training of assessors)	
5			and a description of study instruments (eg,	
6			questionnaires, laboratory tests) along with their	
7			reliability and validity, if known. Reference to	
8			where data collection forms can be found, if not	
9			in the protocol	
10				
11	Data collection	#18b	Plans to promote participant retention and	n/a only 1
12	plan: retention		complete follow-up, including list of any outcome	intervention moment
13			data to be collected for participants who	
14			discontinue or deviate from intervention protocols	
15				
16	Data management	#19	Plans for data entry, coding, security, and	10-11
17			storage, including any related processes to	
18			promote data quality (eg, double data entry;	
19			range checks for data values). Reference to	
20			where details of data management procedures	
21			can be found, if not in the protocol	
22				
23	Statistics: outcomes	#20a	Statistical methods for analysing primary and	10-11
24			secondary outcomes. Reference to where other	
25			details of the statistical analysis plan can be	
26			found, if not in the protocol	
27				
28	Statistics: additional	#20b	Methods for any additional analyses (eg,	10-11
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1	analyses	subgroup and adjusted analyses)	
2			
3	Statistics: analysis	#20c	Definition of analysis population relating to
4			10-11
5	population and	protocol non-adherence (eg, as randomised	
6	missing data	analysis), and any statistical methods to handle	
7		missing data (eg, multiple imputation)	
8			
9			
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11			
12			
13	Methods:		
14			
15	Monitoring		
16			
17			
18	Data monitoring:	#21a	Composition of data monitoring committee
19			n/a
20	formal committee	(DMC); summary of its role and reporting	
21		structure; statement of whether it is independent	
22		from the sponsor and competing interests; and	
23		reference to where further details about its	
24		charter can be found, if not in the protocol.	
25		Alternatively, an explanation of why a DMC is not	
26		needed	
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38	Data monitoring:	#21b	Description of any interim analyses and stopping
39			11
40	interim analysis	guidelines, including who will have access to	
41		these interim results and make the final decision	
42		to terminate the trial	
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47	Harms	#22	Plans for collecting, assessing, reporting, and
48			11
49		managing solicited and spontaneously reported	
50		adverse events and other unintended effects of	
51		trial interventions or trial conduct	
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57	Auditing	#23	Frequency and procedures for auditing trial
58			11
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1			conduct, if any, and whether the process will be	
2				
3			independent from investigators and the sponsor	
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6	Ethics and			
7				
8	dissemination			
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11	Research ethics	#24	Plans for seeking research ethics committee /	12
12				
13	approval		institutional review board (REC / IRB) approval	
14				
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16	Protocol	#25	Plans for communicating important protocol	12
17				
18	amendments		modifications (eg, changes to eligibility criteria,	
19			outcomes, analyses) to relevant parties (eg,	
20			investigators, REC / IRBs, trial participants, trial	
21			registries, journals, regulators)	
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28	Consent or assent	#26a	Who will obtain informed consent or assent from	6
29			potential trial participants or authorised	
30			surrogates, and how (see Item 32)	
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36	6Consent or assent:	#26b	Additional consent provisions for collection and	n/a
37				
38	ancillary studies		use of participant data and biological specimens	
39			in ancillary studies, if applicable	
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44	Confidentiality	#27	How personal information about potential and	10
45			enrolled participants will be collected, shared,	
46			and maintained in order to protect confidentiality	
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51			before, during, and after the trial	
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54	Declaration of	#28	Financial and other competing interests for	12-13
55				
56	interests		principal investigators for the overall trial and	
57				
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		each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	12
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and	n/a model consent in fully in Dutch and

1		authorised surrogates	will therefore not be
2			
3			shared
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6	Biological	#33 Plans for collection, laboratory evaluation, and	n/a
7			
8	specimens	storage of biological specimens for genetic or	
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10		molecular analysis in the current trial and for	
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12		future use in ancillary studies, if applicable	
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16	Notes:		
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19		• 11b: n/a, patients can withdraw, but intervention will not be modified. Doses can not be changed.	
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22		• 11c: n/a there is only 1 intervention (during surgery) that a patient has to adhere to.	
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25		• 17b: n/a surgeons are always unblinded	
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28		• 18b: n/a only 1 intervention moment	
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30			
31		• 32: n/a model consent in fully in Dutch and will therefore not be shared The SPIRIT Explanation	
32			
33		and Elaboration paper is distributed under the terms of the Creative Commons Attribution	
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35		License CC-BY-NC. This checklist was completed on 09. March 2021 using	
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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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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology, Oncology
Keywords:	SURGERY, Gastrointestinal imaging < RADIOLOGY & IMAGING, Gastrointestinal tumours < ONCOLOGY, Inflammatory bowel disease < GASTROENTEROLOGY

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Manuscripts

AVOID; a Phase III, Randomised Controlled Trial Using Indocyanine Green for the Prevention of Anastomotic Leakage in Colorectal Surgery

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Word count: 2671

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 (FGBA) group and the Conventional Bowel Anastomosis (CBA) group. The primary endpoint is clinically relevant AL (defined as requiring active therapeutic intervention or re-operation) 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. The results of this study will be reported through peer-reviewed publications and conference presentations.

Trial registration numbers: NCT04712032 and NL7502

Keywords: bowel perfusion, near infrared fluorescence, indocyanine green, colorectal surgery, colorectal cancer, inflammatory bowel disease

Article Summary

Strengths and limitations of this study

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

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Introduction

Anastomotic leakage (AL) is a major complication after colorectal surgery, accounting for considerable morbidity and mortality.[1-6] 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.[4-15] The occurrence of AL often has a multifactorial cause, including risk factors such as tumour location, level of anastomosis, male gender, high ASA score, comorbidities, smoking, obesity and (neoadjuvant) radiotherapy.[3 4 6 11 13 14 16]

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.[17-19] 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.[20] Though useful, these clinical assessments have proven to have a low predictive value for AL which emphasises the urge for a better diagnostic test.[21]

A promising diagnostic tool is intraoperative near-infrared (NIR) fluorescence imaging. This technique combines a fluorescent contrast agent, e.g. indocyanine green (ICG), and a dedicated NIR imaging system.[22] The intravenous injection of ICG has proven to be a feasible and reproducible application for real-time perfusion assessment.[23-25] ICG was introduced by Fox et al. in 1957 and is currently used for a variety of diagnostic indications.[26] 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.[27]
Moreover, it is cleared quickly by the liver and has low toxicity.[28]

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.[29-32] Moreover, several systematic reviews support this promising results concerning the prevention of AL [33 34]. 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.[35] 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 group (CBA). Patients in the FGBA group will receive at least one dose of 5 milligram ICG, up to a maximum of 3 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 emphasized 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.[36]

Sample size calculation

The power analysis was performed based on Dutch national AL percentages, derived from the Dutch ColoRectal Audit (DCRA).[37] It is hypothesized 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.[38]

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 jeopardizing the patients

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well-being or the study objectives (following a detailed medical history and physical examination).

Randomisation

After inclusion in the study (i.e., 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 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 Inc.,

Sunnyvale, CA, United States of America). 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 minute 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.[39] Grade B (requiring active therapeutic intervention but manageable without re-operation) and C AL (requiring re-operation) will be considered clinically relevant. The assessment of AL will be based on the evaluation of clinical features and subsequent CT scan at the judgment of the attending surgeon. No routine CT scans will be performed for AL assessment.

Secondary outcomes

1. 30-day clinically relevant AL
2. 30- and 90-day all-cause postoperative complications
3. 30- and 90-day mortality; all-cause and AL related
4. 30- 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 center 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 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 standardization of the technique.

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.

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 Leiden University Medical Centre (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 August 1st 2021, 352 patients were included in 6 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-Square 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 2-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.

Sub-group analysis will be conducted by separately assessing patients with 1. colon and rectal resections, 2. left 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 indocyanine green 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.

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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 standardized 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 optimized 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).

ETHICS AND DISSEMINATION

The study was approved by the certified Medical Ethics Review Committee Leiden, Den Haag, Delft (METC-LDD) on 11 November 2019 under identifier P19.079, and feasibility

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3 declarations as required by Dutch law, were obtained for the remaining hospitals. The
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5 protocol's current version (2.0) is dated 26 March 2020. The first patient was recruited on 2
6
7 July 2020 in LUMC. Six centres are currently enrolling patients. Protocol amendments will
8
9 first be reviewed by the METC-LDD and after approval be shared with the participating
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11 centres for local feasibility declarations.
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16 This study was prospectively registered at the Netherlands trial register (NL7502) and after
17
18 the first inclusion registered at clinicaltrials.gov (NCT04712032). A manuscript with the
19
20 results of this study will be published in a peer-reviewed journal. Moreover, the results will
21
22 be shared via conference presentations.
23
24

25 26 **AUTHOR CONTRIBUTIONS**

27
28 RM, RF, OB, JB, EM, JM, KB, AV and DH all contributed to the study concept and design. HP
29
30 was responsible for the statistical analysis plan and the sample size calculation. RM, RF and
31
32 OB prepared the manuscript. JM, AV and DH supervised the manuscript preparation. All
33
34 authors and members of the AVOID study group reviewed the manuscript before
35
36 submission.
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42 43 **FUNDING STATEMENT**

44
45 This research is funded by an Olympus Support Grant (2019-03-0077). The funder will have
46
47 no role in the conduct of the study; collection, management, analysis and interpretation of
48
49 the data; and decision to submit the manuscript for publication.
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53 54 **COMPETING INTERESTS STATEMENT**

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56 AV and LS are members of the Diagnostic Green advisory board. All other authors declare to
57
58 have no competing interest concerning this work.
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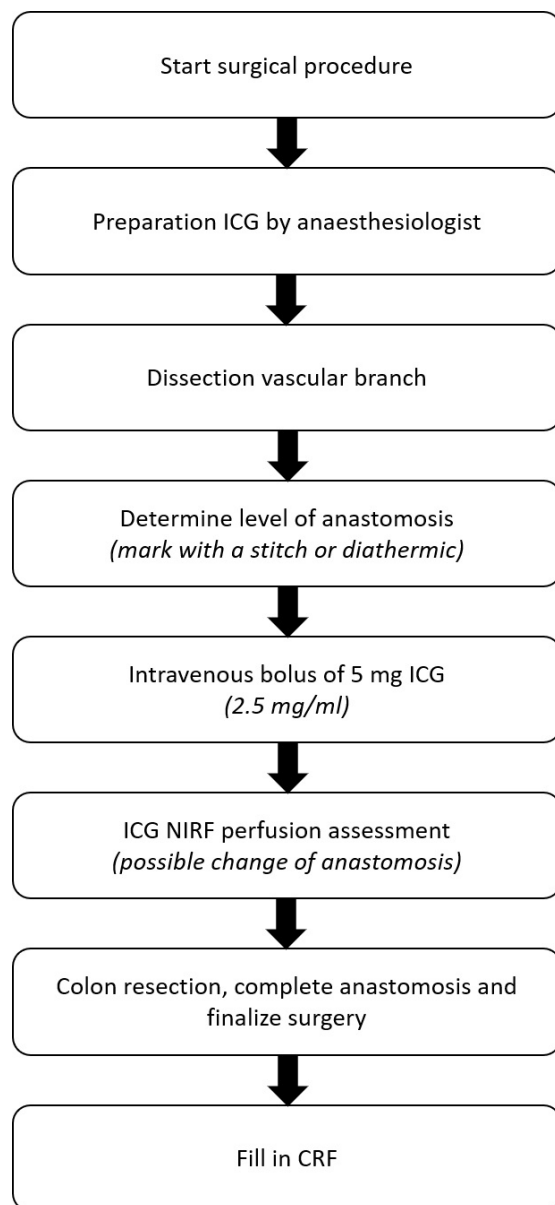


Figure 1 Surgical flowchart
ICG indocyanine green, NIRF Near-infrared, CRF case report form
13x28mm (1200 x 1200 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

	Reporting Item	Page Number
Administrative information		
Title	#1 Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a Trial identifier and registry name. If not yet	2

1		registered, name of intended registry	
2			
3			
4	Trial registration:	#2b All items from the World Health Organization	5-11
5			
6	data set	Trial Registration Data Set	
7			
8			
9	Protocol version	#3 Date and version identifier	12
10			
11			
12	Funding	#4 Sources and types of financial, material, and	12
13			
14		other support	
15			
16			
17	Roles and	#5a Names, affiliations, and roles of protocol	12
18			
19	responsibilities:	contributors	
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21	contributorship		
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25	Roles and	#5b Name and contact information for the trial	1
26			
27	responsibilities:	sponsor	
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29	sponsor contact		
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31	information		
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35	Roles and	#5c Role of study sponsor and funders, if any, in	12
36			
37	responsibilities:	study design; collection, management, analysis,	
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39	sponsor and funder	and interpretation of data; writing of the report;	
40			
41		and the decision to submit the report for	
42			
43		publication, including whether they will have	
44			
45		ultimate authority over any of these activities	
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49	Roles and	#5d Composition, roles, and responsibilities of the	10-11
50			
51	responsibilities:	coordinating centre, steering committee,	
52			
53	committees	endpoint adjudication committee, data	
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55		management team, and other individuals or	
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groups overseeing the trial, if applicable (see
Item 21a for data monitoring committee)

Introduction

Background and [#6a](#) Description of research question and justification
rationale for undertaking the trial, including summary of
relevant studies (published and unpublished)
examining benefits and harms for each
intervention

Background and [#6b](#) Explanation for choice of comparators
rationale: choice of
comparators

Objectives [#7](#) Specific objectives or hypotheses

Trial design [#8](#) Description of trial design including type of trial
(eg, parallel group, crossover, factorial, single
group), allocation ratio, and framework (eg,
superiority, equivalence, non-inferiority,
exploratory)

Methods:

Participants,
interventions, and
outcomes

Study setting [#9](#) Description of study settings (eg, community
clinic, academic hospital) and list of countries

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1		where data will be collected. Reference to where	
2		list of study sites can be obtained	
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6	Eligibility criteria	#10 Inclusion and exclusion criteria for participants. If	7
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8		applicable, eligibility criteria for study centres and	
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10		individuals who will perform the interventions (eg,	
11		surgeons, psychotherapists)	
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16	Interventions:	#11a Interventions for each group with sufficient detail	8-9
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18	description	to allow replication, including how and when they	
19			
20		will be administered	
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23	Interventions:	#11b Criteria for discontinuing or modifying allocated	n/a, patients can
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25	modifications	interventions for a given trial participant (eg, drug	withdraw, but
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27		dose change in response to harms, participant	intervention will not
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29		request, or improving / worsening disease)	be modified. Doses
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31			can not be changed.
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35	Interventions:	#11c Strategies to improve adherence to intervention	n/a there is only 1
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37	adherence	protocols, and any procedures for monitoring	intervention (during
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39		adherence (eg, drug tablet return; laboratory	surgery) that a
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41		tests)	patient has to
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45			adhere to.
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48	Interventions:	#11d Relevant concomitant care and interventions that	8-9
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50	concomitant care	are permitted or prohibited during the trial	
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53	Outcomes	#12 Primary, secondary, and other outcomes,	9
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55		including the specific measurement variable (eg,	
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57		systolic blood pressure), analysis metric (eg,	
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		change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size
Methods:		
Assignment of interventions (for controlled trials)		
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce

1	Data collection plan	#18a	Plans for assessment and collection of outcome,	10
2			baseline, and other trial data, including any	
3			related processes to promote data quality (eg,	
4			duplicate measurements, training of assessors)	
5			and a description of study instruments (eg,	
6			questionnaires, laboratory tests) along with their	
7			reliability and validity, if known. Reference to	
8			where data collection forms can be found, if not	
9			in the protocol	
10				
11	Data collection	#18b	Plans to promote participant retention and	n/a only 1
12	plan: retention		complete follow-up, including list of any outcome	intervention moment
13			data to be collected for participants who	
14			discontinue or deviate from intervention protocols	
15				
16	Data management	#19	Plans for data entry, coding, security, and	10-11
17			storage, including any related processes to	
18			promote data quality (eg, double data entry;	
19			range checks for data values). Reference to	
20			where details of data management procedures	
21			can be found, if not in the protocol	
22				
23	Statistics: outcomes	#20a	Statistical methods for analysing primary and	10-11
24			secondary outcomes. Reference to where other	
25			details of the statistical analysis plan can be	
26			found, if not in the protocol	
27				
28	Statistics: additional	#20b	Methods for any additional analyses (eg,	10-11
29				

Page 29 of 32		BMJ Open	
1	analyses	subgroup and adjusted analyses)	
2			
3	Statistics: analysis	#20c	Definition of analysis population relating to
4			
5	population and		protocol non-adherence (eg, as randomised
6			
7	missing data		analysis), and any statistical methods to handle
8			
9			missing data (eg, multiple imputation)
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13	Methods:		
14			
15	Monitoring		
16			
17			
18	Data monitoring:	#21a	Composition of data monitoring committee
19			
20	formal committee		(DMC); summary of its role and reporting
21			
22			structure; statement of whether it is independent
23			
24			from the sponsor and competing interests; and
25			
26			reference to where further details about its
27			
28			charter can be found, if not in the protocol.
29			
30			Alternatively, an explanation of why a DMC is not
31			
32			needed
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38	Data monitoring:	#21b	Description of any interim analyses and stopping
39			
40	interim analysis		guidelines, including who will have access to
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42			these interim results and make the final decision
43			
44			to terminate the trial
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46			
47	Harms	#22	Plans for collecting, assessing, reporting, and
48			
49			managing solicited and spontaneously reported
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51			adverse events and other unintended effects of
52			
53			trial interventions or trial conduct
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57	Auditing	#23	Frequency and procedures for auditing trial
58			
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60			

conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and	12-13

1		each study site	
2			
3			
4	Data access	#29 Statement of who will have access to the final	10
5		trial dataset, and disclosure of contractual	
6		agreements that limit such access for	
7		investigators	
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13	Ancillary and post	#30 Provisions, if any, for ancillary and post-trial care,	n/a
14	trial care	and for compensation to those who suffer harm	
15		from trial participation	
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21	Dissemination	#31a Plans for investigators and sponsor to	12
22	policy: trial results	communicate trial results to participants,	
23		healthcare professionals, the public, and other	
24		relevant groups (eg, via publication, reporting in	
25		results databases, or other data sharing	
26		arrangements), including any publication	
27		restrictions	
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38	Dissemination	#31b Authorship eligibility guidelines and any intended	12
39	policy: authorship	use of professional writers	
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42			
43	Dissemination	#31c Plans, if any, for granting public access to the full	n/a
44	policy: reproducible	protocol, participant-level dataset, and statistical	
45		code	
46	research		
47			
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51	Appendices		
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54	Informed consent	#32 Model consent form and other related	n/a model consent
55	materials	documentation given to participants and	in fully in Dutch and
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authorised surrogates

will therefore not be

shared

Biological [#33](#) Plans for collection, laboratory evaluation, and
specimens storage of biological specimens for genetic or
molecular analysis in the current trial and for
future use in ancillary studies, if applicable

n/a

Notes:

- 11b: n/a, patients can withdraw, but intervention will not be modified. Doses can not be changed.
- 11c: n/a there is only 1 intervention (during surgery) that a patient has to adhere to.
- 17b: n/a surgeons are always unblinded
- 18b: n/a only 1 intervention moment
- 32: n/a model consent in fully in Dutch and will therefore not be shared The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 09. March 2021 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

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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Keywords:	SURGERY, Gastrointestinal imaging < RADIOLOGY & IMAGING, Gastrointestinal tumours < ONCOLOGY, Inflammatory bowel disease < GASTROENTEROLOGY

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AVOID; a Phase III, Randomised Controlled Trial Using Indocyanine Green for the Prevention of Anastomotic Leakage in Colorectal Surgery

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- * Members of the AVOID study group are listed in appendix A

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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 (FGBA) group and the Conventional Bowel Anastomosis (CBA) group. The primary endpoint is clinically relevant AL (defined as requiring active therapeutic intervention or re-operation) 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. The results of this study will be reported through peer-reviewed publications and conference presentations.

Trial registration numbers: NCT04712032 and NL7502

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Keywords: bowel perfusion, near infrared fluorescence, indocyanine green, colorectal surgery, colorectal cancer, inflammatory bowel disease

Article Summary

Strengths and limitations of this study

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

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59 Introduction

60 Anastomotic leakage (AL) is a major complication after colorectal surgery, accounting for
61 considerable morbidity and mortality.[1-6] The incidence of AL in colorectal surgery ranges
62 from 2.4 to 11% in colon cases and up to 23.3% in rectal cancer surgery.[4-15] The occurrence
63 of AL often has a multifactorial cause, including risk factors such as tumour location, level of
64 anastomosis, male gender, high ASA score, comorbidities, smoking, obesity and
65 (neoadjuvant) radiotherapy.[3 4 6 11 13 14 16]

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

75 A promising diagnostic tool is intraoperative near-infrared (NIR) fluorescence imaging. This
76 technique combines a fluorescent contrast agent, e.g. indocyanine green (ICG), and a
77 dedicated NIR imaging system.[22] The intravenous injection of ICG has proven to be a
78 feasible and reproducible application for real-time perfusion assessment.[23-25] ICG was
79 introduced by Fox et al. in 1957 and is currently used for a variety of diagnostic
80 indications.[26] Diluted and intravenously injected ICG, with a peak emission at 820 nm, is

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invisible for the naked eye and will therefore not interfere with the surgical field.[27]

Moreover, it is cleared quickly by the liver and has low toxicity.[28]

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.[29-32] Moreover, several systematic reviews support this promising results concerning the prevention of AL [33 34]. 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.[35] 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.

103 Hypothesis

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

107 Study design

108 In this multicentre randomised controlled trial, patients will be allocated to two groups: the
109 Fluorescence Guided Bowel Anastomosis group (FGBA) or the Conventional Bowel
110 Anastomosis group (CBA). Patients in the FGBA group will receive at least one dose of 5
111 milligram ICG, up to a maximum of 3 doses, to assess bowel perfusion. Patients in the CBA
112 group will not receive any study related interventions and will be treated according to
113 standard of care. The allocated treatment result is not blinded for the surgeon performing
114 the procedure. Patients will be unblinded after the procedure.

115 Setting

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

118 Participants

119 All patients scheduled for laparoscopic or robotic-assisted colorectal surgery (malignant and
120 benign indications) with primary anastomosis will be screened for eligibility during
121 multidisciplinary team meetings and, when eligible for participation, informed about the
122 study by their attending physician. It will be emphasized that a patient can withdraw from
123 the study at any given moment without having to offer any reason. The fundamental

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124 concepts outlined in the Declaration of Helsinki will be followed during the execution of the
125 trial.[36]

126 **Sample size calculation**

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

132 **Inclusion criteria**

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

138 **Exclusion criteria**

139 A potential patient who meets any of the following criteria will be excluded from
140 participation in this study: known allergy or history of adverse reaction to ICG, iodine or
141 iodine dyes, severe liver or kidney insufficiency, hyperthyroidism or a benign thyroid
142 tumour, pregnant or breastfeeding women, scheduled for emergency surgery, palliative
143 surgery or terminally ill, scheduled for a defunctioning stoma, taking phenobarbital,
144 phenylbutazone, primidone, phenytoin, haloperidol, nitrofurantoin, and probenecid, or any
145 other condition that the investigator considers to be potentially jeopardizing the patients

146 well-being or the study objectives (following a detailed medical history and physical
147 examination).

148 **Randomisation**

149 After inclusion in the study (i.e., after written informed consent is obtained), patients will be
150 randomised to the FGBA or the CBA group. Randomisation will be performed online via
151 Castor EDC (Castor, Amsterdam, the Netherlands) with variable block sizes and stratified by
152 institute. The allocated treatment result is not blinded for the surgeon performing the
153 procedure. Patients will be unblinded after the surgical procedure.

154 **Intervention**

155 Patients in the CBA group will undergo laparoscopic or robotic colorectal resection
156 according to standard of care using conventional methods to assess the integrity and
157 viability of the anastomosis. Patients in the FGBA group will undergo the same standard of
158 care surgical procedure as patients in the CBA group; however, in addition to the
159 conventional methods, NIR fluorescence imaging with ICG will be performed to assess the
160 bowel perfusion at the anastomosis side. All surgeries, in both arms, will be performed by
161 an attending surgeon. NIR fluorescence imaging with ICG will be performed as follows
162 (Figure 1): after dissection of the vascular branch, the preferred level of anastomoses
163 (proximally and distally) will be highlighted by a stitch or diathermic mark in the adjacent
164 mesocolon or mesorectum. Then, 5 mg ICG (2.5 mg/ml, Diagnostic Green, Aschheim,
165 Germany), followed by 10 ml saline flush, will be injected intravenously by the
166 anaesthesiologist. Within a few minutes, the anastomotic microvascularisation of both
167 bowel ends will be assessed using the Olympus Medical Imaging Video System and
168 Laparoscope (Olympus, Leiderdorp, the Netherlands) or Da Vinci Firefly (Intuitive Inc.,

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Sunnyvale, CA, United States of America). 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 minute 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.[39] Grade B (requiring active therapeutic intervention but manageable without re-operation) and C AL (requiring re-operation) 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. Post-operative blood tests, radiologic

192 assessment and subsequent assessment of AL will be based on local protocols and the
193 judgement of the local surgical team.

194 *Secondary outcomes*

- 195 1. 30-day clinically relevant AL
- 196 2. 30- and 90-day all-cause postoperative complications
- 197 3. 30- and 90-day mortality; all-cause and AL related
- 198 4. 30- and 90-day reinterventions; surgical and non-surgical
- 199 5. Total surgical time of primary surgery
- 200 6. Postoperative length of hospital stay; primary stay and readmittance within 90 days
- 201 7. Readmittance; all-cause and AL related

203 **Training**

204 Prior to their first inclusion, surgeons and other involved hospital staff of the participating
205 center will be trained during a site initiation visit by the principal investigator or one of the
206 coordinating investigators. If needed, training with the Olympus Medical Imaging Video
207 System and Laparoscope or Da Vinci Firefly will be provided by either Olympus or Intuitive.
208 Surgeons are invited to observe surgical procedures, using NIR fluorescence imaging with
209 ICG for intraoperative assessment of bowel perfusion, in the LUMC. One of the coordinating
210 investigators, with a broad experience in fluorescence-guided surgery, will assist all
211 participating surgeons during their first number of cases to ensure standardization of the
212 technique.

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

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

225 **Data validation and management**

226 Patient data will be registered coded and analysed by comparing the FGBA group with the
227 CBA group. Only the local investigators will have access to local source data after informed
228 consent is given. The research group from Leiden University Medical Centre (LUMC) will
229 have access to all coded data in the Castor EDC database.

230 **Study timeline**

231 Patients have been included in the study from July 2020, starting in the LUMC. As per
232 August 1st 2021, 352 patients were included in 6 different hospitals. With a mean inclusion
233 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-Square 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 2-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.

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254 Sub-group analysis will be conducted by separately assessing patients with 1. colon and rectal
255 resections, 2. left and right sided resections, 3. malignant and benign pathology and 4. laparoscopic
256 and robotic-assisted surgery.

257 **Data monitoring**

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

261 **Adverse events**

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

265 **Patient and Public Involvement**

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

272 **EXPECTED LIMITATIONS AND DIFFICULTIES**

273 Intraoperative fluorescence assessment of bowel perfusion is currently a subjective tool.
274 This will most likely influence our results as over 30 different surgeons will interpret the

275 fluorescence output. Quantification of the NIR fluorescence signal would improve
276 standardized assessment of tissue perfusion.

277 Using different NIR platforms (the Olympus Medical Imaging Video System and
278 Laparoscope, and the Da Vinci Firefly) will have some influence on our results as well.

279 Nevertheless, both systems are optimized for the detection of ICG, we therefore think its
280 effect on our study results is minimal.

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

284 ETHICS AND DISSEMINATION

285 The study was approved by the certified Medical Ethics Review Committee Leiden, Den
286 Haag, Delft (METC-LDD) on 11 November 2019 under identifier P19.079, and feasibility
287 declarations as required by Dutch law, were obtained for the remaining hospitals. The
288 protocol's current version (2.0) is dated 26 March 2020. The first patient was recruited on 2
289 July 2020 in LUMC. Six centres are currently enrolling patients. Protocol amendments will
290 first be reviewed by the METC-LDD and after approval be shared with the participating
291 centres for local feasibility declarations.

292 This study was prospectively registered at the Netherlands trial register (NL7502) and after
293 the first inclusion registered at clinicaltrials.gov (NCT04712032). A manuscript with the
294 results of this study will be published in a peer-reviewed journal. Moreover, the results will
295 be shared via conference presentations.

296 AUTHOR CONTRIBUTIONS

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297 RM, RF, OB, JB, EM, JM, KB, AV and DH all contributed to the study concept and design. HP
298 was responsible for the statistical analysis plan and the sample size calculation. RM, RF and
299 OB prepared the manuscript. JM, AV and DH supervised the manuscript preparation. All
300 authors and members of the AVOID study group reviewed the manuscript before
301 submission.

302 **FUNDING STATEMENT**

303 This research is funded by an Olympus Support Grant (2019-03-0077). The funder will have
304 no role in the conduct of the study; collection, management, analysis and interpretation of
305 the data; and decision to submit the manuscript for publication.

306 **COMPETING INTERESTS STATEMENT**

307 AV and LS are members of the Diagnostic Green advisory board. All other authors declare to
308 have no competing interest concerning this work.

310 **FIGURE LEGENDS**

311 Figure 1 Surgical flowchart

312 ICG indocyanine green, NIRF Near-infrared, CRF case report form

313

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428 **List of members of the AVOID study group**

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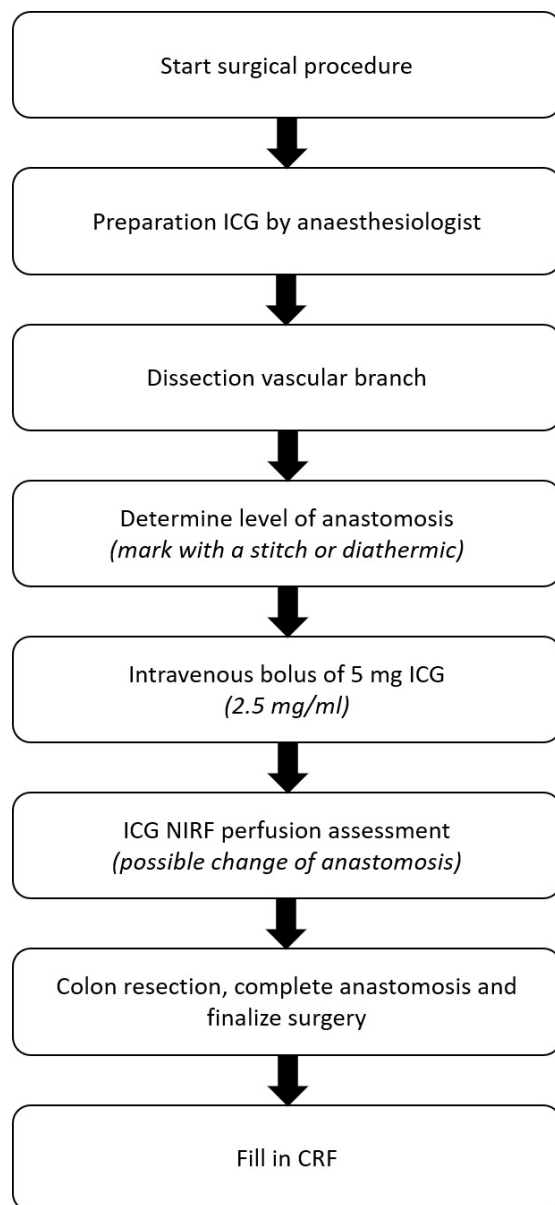


Figure 1 Surgical flowchart
ICG indocyanine green, NIRF Near-infrared, CRF case report form
13x28mm (1200 x 1200 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

	Reporting Item	Page Number
Administrative information		
Title	#1 Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a Trial identifier and registry name. If not yet	2

1		registered, name of intended registry	
2			
3			
4	Trial registration:	#2b All items from the World Health Organization	5-11
5			
6	data set	Trial Registration Data Set	
7			
8			
9	Protocol version	#3 Date and version identifier	12
10			
11			
12	Funding	#4 Sources and types of financial, material, and	12
13			
14		other support	
15			
16			
17	Roles and	#5a Names, affiliations, and roles of protocol	12
18			
19	responsibilities:	contributors	
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21	contributorship		
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24			
25	Roles and	#5b Name and contact information for the trial	1
26			
27	responsibilities:	sponsor	
28			
29	sponsor contact		
30			
31	information		
32			
33			
34			
35	Roles and	#5c Role of study sponsor and funders, if any, in	12
36			
37	responsibilities:	study design; collection, management, analysis,	
38			
39	sponsor and funder	and interpretation of data; writing of the report;	
40			
41		and the decision to submit the report for	
42			
43		publication, including whether they will have	
44			
45		ultimate authority over any of these activities	
46			
47			
48			
49	Roles and	#5d Composition, roles, and responsibilities of the	10-11
50			
51	responsibilities:	coordinating centre, steering committee,	
52			
53	committees	endpoint adjudication committee, data	
54			
55		management team, and other individuals or	
56			
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groups overseeing the trial, if applicable (see
Item 21a for data monitoring committee)

Introduction

Background and [#6a](#) Description of research question and justification
rationale for undertaking the trial, including summary of
relevant studies (published and unpublished)
examining benefits and harms for each
intervention

Background and [#6b](#) Explanation for choice of comparators
rationale: choice of
comparators

Objectives [#7](#) Specific objectives or hypotheses

Trial design [#8](#) Description of trial design including type of trial
(eg, parallel group, crossover, factorial, single
group), allocation ratio, and framework (eg,
superiority, equivalence, non-inferiority,
exploratory)

Methods:

Participants,
interventions, and
outcomes

Study setting [#9](#) Description of study settings (eg, community
clinic, academic hospital) and list of countries

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1		where data will be collected. Reference to where	
2		list of study sites can be obtained	
3			
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5			
6	Eligibility criteria	#10 Inclusion and exclusion criteria for participants. If	7
7			
8		applicable, eligibility criteria for study centres and	
9			
10		individuals who will perform the interventions (eg,	
11		surgeons, psychotherapists)	
12			
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16	Interventions:	#11a Interventions for each group with sufficient detail	8-9
17			
18	description	to allow replication, including how and when they	
19			
20		will be administered	
21			
22			
23	Interventions:	#11b Criteria for discontinuing or modifying allocated	n/a, patients can
24			
25	modifications	interventions for a given trial participant (eg, drug	withdraw, but
26			
27		dose change in response to harms, participant	intervention will not
28			
29		request, or improving / worsening disease)	be modified. Doses
30			
31			can not be changed.
32			
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35	Interventions:	#11c Strategies to improve adherence to intervention	n/a there is only 1
36			
37	adherence	protocols, and any procedures for monitoring	intervention (during
38			
39		adherence (eg, drug tablet return; laboratory	surgery) that a
40			
41		tests)	patient has to
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45			adhere to.
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48	Interventions:	#11d Relevant concomitant care and interventions that	8-9
49			
50	concomitant care	are permitted or prohibited during the trial	
51			
52			
53	Outcomes	#12 Primary, secondary, and other outcomes,	9
54			
55		including the specific measurement variable (eg,	
56			
57		systolic blood pressure), analysis metric (eg,	
58			
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- change from baseline, final value, time to event),
 method of aggregation (eg, median, proportion),
 and time point for each outcome. Explanation of
 the clinical relevance of chosen efficacy and
 harm outcomes is strongly recommended
- Participant timeline [#13](#) Time schedule of enrolment, interventions
 (including any run-ins and washouts),
 assessments, and visits for participants. A
 schematic diagram is highly recommended (see
 Figure)
- Sample size [#14](#) Estimated number of participants needed to
 achieve study objectives and how it was
 determined, including clinical and statistical
 assumptions supporting any sample size
 calculations
- Recruitment [#15](#) Strategies for achieving adequate participant
 enrolment to reach target sample size
- Methods:**
- Assignment of
 interventions (for
 controlled trials)**
- Allocation: [#16a](#) Method of generating the allocation sequence
 (eg, computer-generated random numbers), and
 generation list of any factors for stratification. To reduce

1		predictability of a random sequence, details of	
2		any planned restriction (eg, blocking) should be	
3		provided in a separate document that is	
4		unavailable to those who enrol participants or	
5		assign interventions	
6			
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13	Allocation	#16b Mechanism of implementing the allocation	
14			
15	concealment	sequence (eg, central telephone; sequentially	
16		numbered, opaque, sealed envelopes),	
17	mechanism	describing any steps to conceal the sequence	
18		until interventions are assigned	
19			
20			
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24			
25	Allocation:	#16c Who will generate the allocation sequence, who	
26			
27	implementation	will enrol participants, and who will assign	
28		participants to interventions	
29			
30			
31			
32	Blinding (masking)	#17a Who will be blinded after assignment to	
33			
34		interventions (eg, trial participants, care	
35		providers, outcome assessors, data analysts),	
36		and how	
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42	Blinding (masking):	#17b If blinded, circumstances under which unblinding	n/a surgeons are
43			
44	emergency	is permissible, and procedure for revealing a	always unblinded
45			
46	unblinding	participant's allocated intervention during the trial	
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50	Methods: Data		
51			
52	collection,		
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54	management, and		
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56	analysis		
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1	Data collection plan	#18a	Plans for assessment and collection of outcome,	10
2			baseline, and other trial data, including any	
3			related processes to promote data quality (eg,	
4			duplicate measurements, training of assessors)	
5			and a description of study instruments (eg,	
6			questionnaires, laboratory tests) along with their	
7			reliability and validity, if known. Reference to	
8			where data collection forms can be found, if not	
9			in the protocol	
10				
11	Data collection	#18b	Plans to promote participant retention and	n/a only 1
12	plan: retention		complete follow-up, including list of any outcome	intervention moment
13			data to be collected for participants who	
14			discontinue or deviate from intervention protocols	
15				
16	Data management	#19	Plans for data entry, coding, security, and	10-11
17			storage, including any related processes to	
18			promote data quality (eg, double data entry;	
19			range checks for data values). Reference to	
20			where details of data management procedures	
21			can be found, if not in the protocol	
22				
23	Statistics: outcomes	#20a	Statistical methods for analysing primary and	10-11
24			secondary outcomes. Reference to where other	
25			details of the statistical analysis plan can be	
26			found, if not in the protocol	
27				
28	Statistics: additional	#20b	Methods for any additional analyses (eg,	10-11
29				

Page 29 of 32		BMJ Open	
1	analyses	subgroup and adjusted analyses)	
2			
3	Statistics: analysis	#20c	Definition of analysis population relating to
4			10-11
5	population and		
6			protocol non-adherence (eg, as randomised
7			
8	missing data		analysis), and any statistical methods to handle
9			
10			missing data (eg, multiple imputation)
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13	Methods:		
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15	Monitoring		
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17			
18	Data monitoring:	#21a	Composition of data monitoring committee
19			n/a
20	formal committee		(DMC); summary of its role and reporting
21			
22			structure; statement of whether it is independent
23			
24			from the sponsor and competing interests; and
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26			reference to where further details about its
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28			charter can be found, if not in the protocol.
29			
30			Alternatively, an explanation of why a DMC is not
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32			needed
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38	Data monitoring:	#21b	Description of any interim analyses and stopping
39			11
40	interim analysis		guidelines, including who will have access to
41			
42			these interim results and make the final decision
43			
44			to terminate the trial
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47	Harms	#22	Plans for collecting, assessing, reporting, and
48			11
49			managing solicited and spontaneously reported
50			
51			adverse events and other unintended effects of
52			
53			trial interventions or trial conduct
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57	Auditing	#23	Frequency and procedures for auditing trial
58			11
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conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and	12-13

1		each study site	
2			
3			
4	Data access	#29 Statement of who will have access to the final	10
5		trial dataset, and disclosure of contractual	
6		agreements that limit such access for	
7		investigators	
8			
9			
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13	Ancillary and post	#30 Provisions, if any, for ancillary and post-trial care,	n/a
14	trial care	and for compensation to those who suffer harm	
15		from trial participation	
16			
17			
18			
19			
20			
21	Dissemination	#31a Plans for investigators and sponsor to	12
22	policy: trial results	communicate trial results to participants,	
23		healthcare professionals, the public, and other	
24		relevant groups (eg, via publication, reporting in	
25		results databases, or other data sharing	
26		arrangements), including any publication	
27		restrictions	
28			
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38	Dissemination	#31b Authorship eligibility guidelines and any intended	12
39	policy: authorship	use of professional writers	
40			
41			
42			
43	Dissemination	#31c Plans, if any, for granting public access to the full	n/a
44	policy: reproducible	protocol, participant-level dataset, and statistical	
45		code	
46	research		
47			
48			
49			
50			
51	Appendices		
52			
53			
54	Informed consent	#32 Model consent form and other related	n/a model consent
55	materials	documentation given to participants and	in fully in Dutch and
56			
57			
58			
59			
60			

authorised surrogates

will therefore not be

shared

Biological

#33

Plans for collection, laboratory evaluation, and

n/a

specimens

storage of biological specimens for genetic or

molecular analysis in the current trial and for

future use in ancillary studies, if applicable

Notes:

- 11b: n/a, patients can withdraw, but intervention will not be modified. Doses can not be changed.
- 11c: n/a there is only 1 intervention (during surgery) that a patient has to adhere to.
- 17b: n/a surgeons are always unblinded
- 18b: n/a only 1 intervention moment
- 32: n/a model consent in fully in Dutch and will therefore not be shared The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 09. March 2021 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](https://www.equator-network.org/) in collaboration with [Penelope.ai](https://www.penelope.ai/)