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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-051144
Article Type:	Protocol
Date Submitted by the Author:	10-Mar-2021
Complete List of Authors:	Meijer, Ruben; Leiden University Medical Center; Centre for Human Drug Research Faber, Robin; Leiden University Medical Center Bijlstra, Okker; Leiden University Medical Center Braak, Jeffrey; Leiden University Medical Center Meershoek-Klein Kranenburg, Elma; Leiden University Medical Center Putter, Hein; Leiden University Medical Center Burggraaf, Koos; Centre for Human Drug Research, Vahrmeijer, Alexander; Leids Universitair Medisch Centrum, Surgery Hilling, Denise; Leiden University Medical Center; Erasmus Medical Center
Keywords:	SURGERY, Gastrointestinal imaging < RADIOLOGY & IMAGING, Gastrointestinal tumours < ONCOLOGY, Inflammatory bowel disease < GASTROENTEROLOGY

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3 **AVOID; a Phase III, Randomised Controlled Trial Using Indocyanine Green for the Prevention**
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5 **of Anastomotic Leakage in Colorectal Surgery**
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8 Ruben P.J. Meijer^{1,2}, Robin A. Faber¹, Okker D. Bijlstra¹, Jeffrey P.B.M. Braak¹, Elma
9
10 Meershoek-Klein Kranenbarg¹, Hein Putter³, Jacobus Burggraaf², Alexander L. Vahrmeijer¹,
11
12 Denise E. Hilling^{1,4,*}, AVOID study group*
13
14
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16
17

18 **Affiliations**
19

- 20 1. Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands
21
22 2. Centre for Human Drug Research, Leiden, the Netherlands
23
24 3. Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden,
25
26 the Netherlands
27
28 4. Department of Surgical Oncology and Gastrointestinal Surgery, Erasmus MC Cancer
29
30 Institute, University Medical Center Rotterdam, the Netherlands
31
32
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35 * Members of the AVOID study group are listed in appendix A
36
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38
39
40
41
42

43 ***Corresponding author**
44

45 D.E. Hilling, MD, PhD
46

47 Department of Surgery
48

49 Leiden University Medical Center
50

51 Leiden, The Netherlands
52

53 E-mail: d.hilling@erasmusmc.nl
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60 **Word count: 2226**

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

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

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

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9 Several cohort studies have investigated the benefit of NIR fluorescence imaging with ICG for
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11 intraoperative assessment of bowel perfusion. Some of these studies have shown that this
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13 technique enables clear visualisation of bowel perfusion within minutes after intravenous
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15 injection of ICG, resulting in reduced leakage rates and hospital stay.[29-32] Moreover,
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17 several systematic reviews support this promising results concerning the prevention of AL. On
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19 the other hand, Kin et al. have shown no benefit by using ICG in preventing AL.[33] Major
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21 drawbacks of these studies are that they were not randomised and did not use clinically
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23 relevant 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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27 to investigate the benefit of intraoperative imaging with ICG for the reduction of AL rate in
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29 colorectal surgery.
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39 **METHODS AND ANALYSIS**

40 41 42 **Primary aim**

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45 The main objective of this study is to assess if ICG-guided perfusion assessment will result in
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47 a reduction of the AL rate within 90 days after surgery. ICG-guided perfusion assessment will
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49 be an adjunct to conventional laparoscopic imaging versus conventional laparoscopic
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51 imaging alone.
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54 55 56 **Hypothesis**

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3 It is hypothesised that intraoperative assessment of bowel perfusion using NIR fluorescence
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6 imaging with ICG will lower the incidence of clinically relevant AL within 90 days after
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8 colorectal resection.
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10 11 **Study design**

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14 In this multicentre randomised controlled trial, patients will be allocated to two groups: the
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16 Fluorescence Guided Bowel Anastomosis group (FGBA) or the Conventional Bowel
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18 Anastomosis group (CBA). Patients in the FGBA group will receive at least one dose of 5
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20 milligram ICG, up to a maximum of 3 doses, to assess bowel perfusion. Patients in the CBA
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22 group will not receive any study related interventions and will be treated according to
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24 standard of care. The allocated treatment result is not blinded for the surgeon performing
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26 the procedure. Patients will be unblinded after the procedure.
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31 32 **Setting**

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35 This study will take place in at least two academic hospitals and multiple large teaching
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37 hospitals in the Netherlands. More centres will be added during the course of the study.
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40 41 **Participants**

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44 All patients scheduled for laparoscopic or robotic-assisted colorectal surgery (malignant and
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46 benign indications) with primary anastomosis will be screened for eligibility during
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48 multidisciplinary team meetings and, when eligible for participation, informed about the
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50 study by their attending physician. It will be emphasized that a patient can withdraw from
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52 the study at any given moment without having to offer any reason. The fundamental
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54 concepts outlined in the Declaration of Helsinki will be followed during the execution of the
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56 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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2
3 administration. Repeated doses may be applicable when, for example, both anastomosis
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5 sides do not fit into the optical field, or when perfusion seems compromised after
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7 anastomosis finalisation. All injections, including the reason(s) for repeated injection(s),
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9 time of administration and consequences of administration, will be documented in the case
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11 report form (CRF).
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16 **Outcome measures**

17 *Primary outcome*

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19 The primary outcome is the rate of clinically relevant AL within 90 days after surgery. This
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21 will be compared between the FGBA group using ICG for perfusion assessment and the
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23 standard of care surgery, CBA group. The definition of clinically relevant AL is derived from
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25 the definition of Rahbari et al.[37] Grade B (requiring active therapeutic intervention but
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27 manageable without re-operation) and C AL (requiring re-operation) will be considered
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29 clinically relevant.
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37 *Secondary outcomes*

- 38 1. 30-day clinically relevant AL
 - 39 2. 30- and 90-day all-cause postoperative complications
 - 40 3. 30- and 90-day mortality; all-cause and AL related
 - 41 4. 30- and 90-day reinterventions; surgical and non-surgical
 - 42 5. Total surgical time of primary surgery
 - 43 6. Postoperative length of hospital stay; primary stay and readmittance within 90 days
 - 44 7. Readmittance; all-cause and AL related
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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

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2
3 Mann-Whitney U test, depending on distribution. All p-values will be 2-sided. A p-value of
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5 less than 0.0492 will indicate a statistically significant difference. All data will be analysed on
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7 an intention-to-treat principle and, when applicable, on a per protocol analysis.
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11 The primary outcome measure, clinically relevant AL within 90 days after surgery, will be
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13 compared using the Mantel-Haenszel test, stratified by centre.
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17 An interim analysis will be conducted after 489 patients have been randomised and reached
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19 the last day of follow-up (day 90). This interim analysis will aim at stopping the study for
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21 futility, if the conditional power for the primary endpoint (clinically relevant AL within 90
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23 days after surgery) with the planned sample size, based on the observed results at the
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25 interim analysis, using the original settings of null and alternative hypothesis, is less than
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27 10%.
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31 If this interim analysis shows efficacy based on the primary endpoint with a nominal alpha
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33 level of 0.0054, the study will be stopped as well. Already included patients will be followed
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35 until the last follow-up moment.
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38 39 40 **Data monitoring**

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42 The study will be monitored for quality and regulatory compliance, by study-independent
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44 LUMC staff. Monitoring frequency will be at least annually, but may be increased depending
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46 on findings.
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49 50 51 **Adverse events**

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

FUNDING STATEMENT

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

COMPETING INTERESTS STATEMENT

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3 AV and LS are members of the Diagnostic Green advisory board. All other authors declare to
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5 have no competing interest concerning this work.
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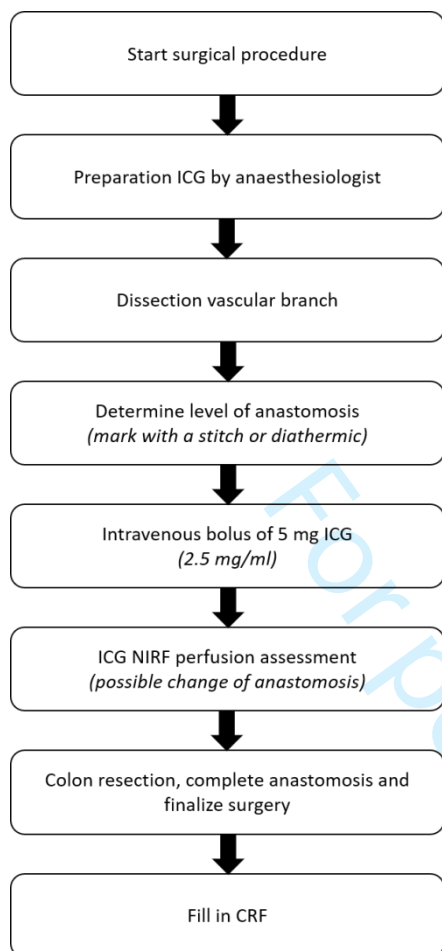
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34 **Figure 1** Surgical flowchart

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

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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)

Tjeerd S. Aukema (HAGA hospital, The Hague, The Netherlands), Coen I.M. Baeten (Groene
Hart Hospital, Gouda, The Netherlands), Johanne G. Bloemen (Catharina Hospital,
Eindhoven, The Netherlands), Annelies Bodegom (Haaglanden Medical Center, The Hague,
The Netherlands), Fran Boersma (Leiden University Medical Center, Leiden, The
Netherlands), Koop Bosscha (Jeroen Bosch Hospital, Den Bosch, The Netherlands), Mark
A.M. Brouwers (HAGA hospital, The Hague, The Netherlands), Esther C.J. Consten (Meander
Medical Center, Amersfoort, The Netherlands), Pascal G. Doornebosch (IJsselland Hospital,
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)

For peer review only

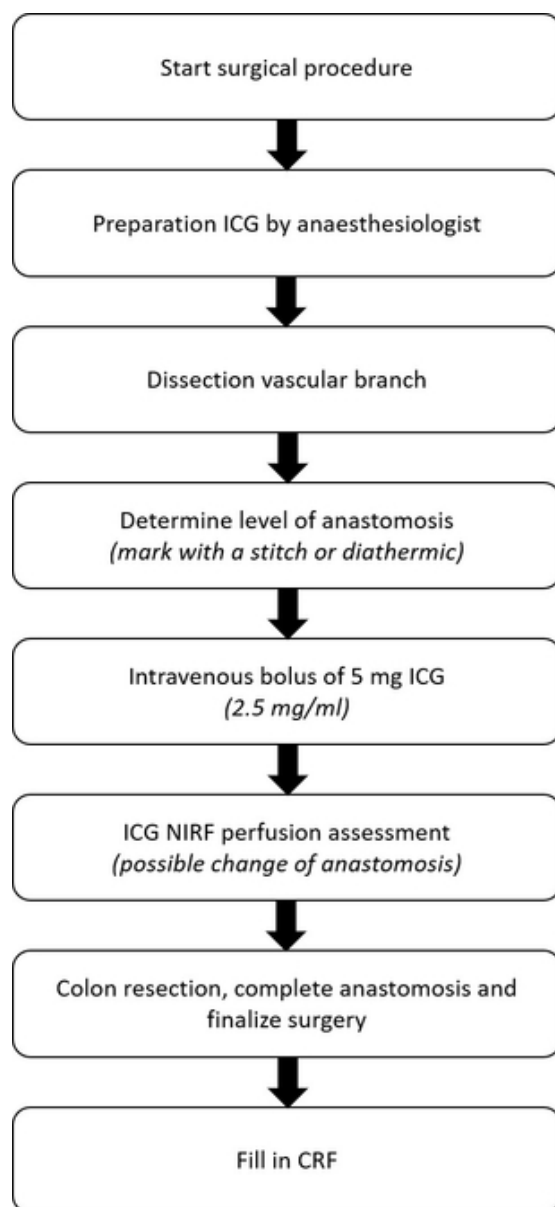


Figure 1 Surgical flowchart
ICG indocyanine green, NIRF Near-infrared, CRF case report form

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	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		other support	
14			
15			
16			
17	Roles and	#5a Names, affiliations, and roles of protocol	12
18			
19	responsibilities:	contributors	
20			
21	contributorship		
22			
23			
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		and interpretation of data; writing of the report;	
39	sponsor and funder	and the decision to submit the report for	
40		publication, including whether they will have	
41		ultimate authority over any of these activities	
42			
43			
44			
45			
46			
47			
48			
49	Roles and	#5d Composition, roles, and responsibilities of the	10-11
50			
51	responsibilities:	coordinating centre, steering committee,	
52		endpoint adjudication committee, data	
53	committees	management team, and other individuals or	
54			
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groups overseeing the trial, if applicable (see
Item 21a for data monitoring committee)

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-6
Objectives	#7	Specific objectives or hypotheses	5
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)	5-11
Methods:			
Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries	6

1		where data will be collected. Reference to where	
2		list of study sites can be obtained	
3			
4			
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			
12		surgeons, psychotherapists)	
13			
14			
15			
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			
33			
34			
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
42			
43			
44			
45			adhere to.
46			
47			
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			
59			
60			

1		change from baseline, final value, time to event),	
2		method of aggregation (eg, median, proportion),	
3		and time point for each outcome. Explanation of	
4		the clinical relevance of chosen efficacy and	
5		harm outcomes is strongly recommended	
6			
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11			
12	Participant timeline	#13 Time schedule of enrolment, interventions	8
13		(including any run-ins and washouts),	
14		assessments, and visits for participants. A	
15		schematic diagram is highly recommended (see	
16		Figure)	
17			
18			
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23			
24	Sample size	#14 Estimated number of participants needed to	10-11
25		achieve study objectives and how it was	
26		determined, including clinical and statistical	
27		assumptions supporting any sample size	
28		calculations	
29			
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36			
37	Recruitment	#15 Strategies for achieving adequate participant	6
38		enrolment to reach target sample size	
39			
40			
41			
42	Methods:		
43			
44	Assignment of		
45	interventions (for		
46	controlled trials)		
47			
48			
49			
50			
51			
52	Allocation:	#16a Method of generating the allocation sequence	8
53	sequence	(eg, computer-generated random numbers), and	
54	generation	list of any factors for stratification. To reduce	
55			
56			
57			
58			
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60			

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			
7			
8			
9			
10			
11			
12			
13	Allocation	#16b Mechanism of implementing the allocation	8
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			
21			
22			
23			
24			
25	Allocation:	#16c Who will generate the allocation sequence, who	6-8
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	8
33		interventions (eg, trial participants, care	
34		providers, outcome assessors, data analysts),	
35		and how	
36			
37			
38			
39			
40			
41			
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	
47			
48			
49			
50	Methods: Data		
51			
52	collection,		
53			
54	management, and		
55			
56	analysis		
57			
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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				

1	analyses		subgroup and adjusted analyses)	
2				
3	Statistics: analysis	#20c	Definition of analysis population relating to	10-11
4	population and		protocol non-adherence (eg, as randomised	
5	missing data		analysis), and any statistical methods to handle	
6			missing data (eg, multiple imputation)	
7				
8	Methods:			
9				
10	Monitoring			
11				
12	Data monitoring:	#21a	Composition of data monitoring committee	n/a
13	formal committee		(DMC); summary of its role and reporting	
14			structure; statement of whether it is independent	
15			from the sponsor and competing interests; and	
16			reference to where further details about its	
17			charter can be found, if not in the protocol.	
18			Alternatively, an explanation of why a DMC is not	
19			needed	
20	Data monitoring:	#21b	Description of any interim analyses and stopping	11
21	interim analysis		guidelines, including who will have access to	
22			these interim results and make the final decision	
23			to terminate the trial	
24				
25	Harms	#22	Plans for collecting, assessing, reporting, and	11
26			managing solicited and spontaneously reported	
27			adverse events and other unintended effects of	
28			trial interventions or trial conduct	
29				
30	Auditing	#23	Frequency and procedures for auditing trial	11
31				

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

Ethics and dissemination

11	Research ethics	#24	Plans for seeking research ethics committee /	12
12			institutional review board (REC / IRB) approval	
13	approval			
16	Protocol	#25	Plans for communicating important protocol	12
17	amendments		modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
29	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
36	6Consent or assent:	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
37	ancillary studies			
44	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
54	Declaration of	#28	Financial and other competing interests for	12-13
55	interests		principal investigators for the overall trial and	

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			
10			
11			
12			
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			
29			
30			
31			
32			
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37			
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			
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			
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authorised surrogates

will therefore not be

shared

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a
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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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-051144.R1
Article Type:	Protocol
Date Submitted by the Author:	17-Sep-2021
Complete List of Authors:	Meijer, Ruben; Leiden University Medical Center; Centre for Human Drug Research Faber, Robin; Leiden University Medical Center Bijlstra, Okker; Leiden University Medical Center Braak, Jeffrey; Leiden University Medical Center Meershoek-Klein Kranenbarg, Elma; Leiden University Medical Center Putter, Hein; Leiden University Medical Center Mieog, J.; Leiden University Medical Center, Surgery Burggraaf, Koos; Centre for Human Drug Research, Vahrmeijer, Alexander; Leids Universitair Medisch Centrum, Surgery Hilling, Denise; Leiden University Medical Center; Erasmus Medical Center
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology, Oncology
Keywords:	SURGERY, Gastrointestinal imaging < RADIOLOGY & IMAGING, Gastrointestinal tumours < ONCOLOGY, Inflammatory bowel disease < GASTROENTEROLOGY

SCHOLARONE™
Manuscripts

1
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3 **AVOID; a Phase III, Randomised Controlled Trial Using Indocyanine Green for the Prevention**
4
5 **of Anastomotic Leakage in Colorectal Surgery**
6
7

8 Ruben P.J. Meijer^{1,2}, Robin A. Faber¹, Okker D. Bijlstra¹, Jeffrey P.B.M. Braak¹, Elma
9
10 Meershoek-Klein Kranenbarg¹, Hein Putter³, J. Sven D. Mieog¹, Koos Burggraaf², Alexander L.
11
12 Vahrmeijer¹, Denise E. Hilling^{1,4,*}, AVOID study group*
13
14
15
16
17

18 **Affiliations**
19

- 20 1. Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands
21
22 2. Centre for Human Drug Research, Leiden, the Netherlands
23
24 3. Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden,
25
26 the Netherlands
27
28 4. Department of Surgical Oncology and Gastrointestinal Surgery, Erasmus MC Cancer
29
30 Institute, University Medical Center Rotterdam, the Netherlands
31
32
33
34
35 * Members of the AVOID study group are listed in appendix A
36
37
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39
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41
42

43 ***Corresponding author**
44

45 D.E. Hilling, MD, PhD
46

47 Department of Surgery
48

49 Leiden University Medical Center
50

51 Leiden, The Netherlands
52

53 E-mail: d.hilling@erasmusmc.nl
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60 **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

1
2
3 **Keywords:** bowel perfusion, near infrared fluorescence, indocyanine green, colorectal
4
5 surgery, colorectal cancer, inflammatory bowel disease
6
7

8
9 **Article Summary**

10
11 **Strengths and limitations of this study**

- 12
13 1. This study is a multicentre randomised controlled trial
14 2. AL is a major complication with huge impact on patient's life
15 3. A clinically relevant endpoint will be used as the primary endpoint
16 4. Quantification of fluorescence-guided bowel perfusion with indocyanine green
17 would be a preferable addition, however its clinical correlation is unclear at this
18 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

1
2
3 invisible for the naked eye and will therefore not interfere with the surgical field.[27]

4
5
6 Moreover, it is cleared quickly by the liver and has low toxicity.[28]

7
8
9 Several cohort studies have investigated the benefit of NIR fluorescence imaging with ICG for
10
11 intraoperative assessment of bowel perfusion. Some of these studies have shown that this
12
13 technique enables clear visualisation of bowel perfusion within minutes after intravenous
14
15 injection of ICG, resulting in reduced leakage rates and hospital stay.[29-32] Moreover,
16
17 several systematic reviews support this promising results concerning the prevention of AL [33
18
19 34]. This has already led to the start of two randomised controlled trials (ICG-COLORAL;
20
21 NCT03602677 and InTACT trial; ISCRN 13334746) which are currently recruiting patients. On the
22
23 other hand, Kin et al. have shown no benefit by using ICG in preventing AL.[35] Major
24
25 drawbacks of these cohort studies are that they were not randomised and did not use
26
27 clinically relevant AL as the primary endpoint. Therefore, we propose AVOID: '*Anastomotic*
28
29 *leakage and Value Of Indocyanine green in Decreasing leakage rates*', a randomised
30
31 controlled trial to investigate the benefit of intraoperative imaging with ICG for the reduction
32
33 of AL rate in colorectal surgery.
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44 **METHODS AND ANALYSIS**

45 46 47 **Primary aim**

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49
50 The main objective of this study is to assess if ICG-guided perfusion assessment will result in
51
52 a reduction of the AL rate within 90 days after surgery. ICG-guided perfusion assessment will
53
54 be an adjunct to conventional laparoscopic imaging versus conventional laparoscopic
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56 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 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

1
2
3 concepts outlined in the Declaration of Helsinki will be followed during the execution of the
4
5 trial.[36]
6
7

8 9 **Sample size calculation**

10
11 The power analysis was performed based on Dutch national AL percentages, derived from the
12 Dutch ColoRectal Audit (DCRA).[37] It is hypothesized that the use of ICG will decrease the
13 AL rate in colorectal surgery from 7 to 3%. With a significance of 0.0492 (adjusted for the
14 interim analysis using the O'Brien-Flemming approach), power of 80%, drop-out of 5% and a
15 control-intervention ratio of 1:1, a sample size of 978 (489:489) patients is needed.[38]
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24 25 **Inclusion criteria**

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27 In order to be eligible to participate in this study, a patient must meet all of the following
28 criteria: aged 18 years and above, scheduled for laparoscopic or robotic-assisted colorectal
29 resection with primary anastomosis, able to communicate in the Dutch language and willing
30 to comply with the study restrictions, and signed informed consent prior to any study-
31 mandated procedure.
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40 41 **Exclusion criteria**

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

7 8 9 **Randomisation**

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11 After inclusion in the study (i.e., after written informed consent is obtained), patients will be
12
13 randomised to the FGBA or the CBA group. Randomisation will be performed online via
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15 Castor EDC (Castor, Amsterdam, the Netherlands) with variable block sizes and stratified by
16
17 institute. The allocated treatment result is not blinded for the surgeon performing the
18
19 procedure. Patients will be unblinded after the surgical procedure.
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24 25 **Intervention**

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27 Patients in the CBA group will undergo laparoscopic or robotic colorectal resection
28
29 according to standard of care using conventional methods to assess the integrity and
30
31 viability of the anastomosis. Patients in the FGBA group will undergo the same standard of
32
33 care surgical procedure as patients in the CBA group; however, in addition to the
34
35 conventional methods, NIR fluorescence imaging with ICG will be performed to assess the
36
37 bowel perfusion at the anastomosis side. All surgeries, in both arms, will be performed by
38
39 an attending surgeon. NIR fluorescence imaging with ICG will be performed as follows
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41
42 (Figure 1): after dissection of the vascular branch, the preferred level of anastomoses
43
44 (proximally and distally) will be highlighted by a stitch or diathermic mark in the adjacent
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46 mesocolon or mesorectum. Then, 5 mg ICG (2.5 mg/ml, Diagnostic Green, Aschheim,
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48 Germany), followed by 10 ml saline flush, will be injected intravenously by the
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50 anaesthesiologist. Within a few minutes, the anastomotic microvascularisation of both
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3 Sunnyvale, CA, United States of America). The level of resection and subsequent
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5 anastomosis may be changed accordingly (with the mesocolic stitch serving as the baseline).
6
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8 During the procedure, the ICG injection (5 mg) may be repeated for a second or third time
9
10 with a 15 minute wash-out period between each administration. Repeated doses may be
11
12 applicable when, for example, both anastomosis sides do not fit into the optical field, or
13
14 when perfusion seems compromised after anastomosis finalisation. All injections, including
15
16 the reason(s) for repeated injection(s), and the consequences of administration, will be
17
18 documented in the case report form (CRF).
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23 The 90-day follow-up is a standard of care follow-up moment in all participating hospitals. It will be
24
25 done either by phone, by videoconference or in person, according to standard of care in the
26
27 participating hospital. Patients who, for any reason, do not visit the hospital 90 days after
28
29 resection, will be contacted by phone and asked for any postoperative complications or
30
31 reinterventions.
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35 **Outcome measures**

36 *Primary outcome*

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38
39 The primary outcome is the rate of clinically relevant AL within 90 days after surgery. This
40
41 will be compared between the FGBA group using ICG for perfusion assessment and the
42
43 standard of care surgery, CBA group. The definition of clinically relevant AL is derived from
44
45 the definition of Rahbari et al.[39] Grade B (requiring active therapeutic intervention but
46
47 manageable without re-operation) and C AL (requiring re-operation) will be considered
48
49 clinically relevant. The assessment of AL will be based on the evaluation of clinical features and
50
51 subsequent CT scan at the judgment of the attending surgeon. No routine CT scans will be
52
53 performed for AL assessment.
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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

1
2
3 addition, in case of a non-planned defunctioning stoma, it will be recorded whether ICG-
4
5 guidance contributed to this decision. All clinical data will be prospectively registered via an
6
7 electronic CRF (eCRF) in a digital database of Castor EDC.
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10 11 **Data validation and management**

12
13
14 Patient data will be registered coded and analysed by comparing the FGBA group with the
15
16 CBA group. Only the local investigators will have access to local source data after informed
17
18 consent is given. The research group from Leiden University Medical Centre (LUMC) will
19
20 have access to all coded data in the Castor EDC database.
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24 25 **Study timeline**

26
27
28 Patients have been included in the study from July 2020, starting in the LUMC. As per
29
30 August 1st 2021, 352 patients were included in 6 different hospitals. With a mean inclusion
31
32 rate of 40 patients per month the anticipated last inclusion will be in the final quarter of
33
34 2022. There is no maximum for the number of centres nor the number of inclusions per
35
36 centre.
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40 41 **Statistical analysis**

42
43
44 The most recent version of SPSS (IBM, Armonk, New York, USA) will be used for statistical
45
46 analysis. Categorical variables of the FGBA and CBA group will be compared by the Chi-
47
48 Square test. Numerical variables will be compared by the independent sample T-test or the
49
50 Mann-Whitney U test, depending on distribution. All p-values will be 2-sided. A p-value of
51
52 less than 0.0492 will indicate a statistically significant difference. All data will be analysed on
53
54 an intention-to-treat principle and, when applicable, on a per protocol analysis.
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3 The primary outcome measure, clinically relevant AL within 90 days after surgery, will be
4 compared using the Mantel-Haenszel test, stratified by centre.
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8 An interim analysis will be conducted after 489 patients have been randomised and reached
9 the last day of follow-up (day 90). This interim analysis will aim at stopping the study for
10 futility, if the conditional power for the primary endpoint (clinically relevant AL within 90
11 days after surgery) with the planned sample size, based on the observed results at the
12 interim analysis, using the original settings of null and alternative hypothesis, is less than
13 10%.
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24 If this interim analysis shows efficacy based on the primary endpoint with a nominal alpha
25 level of 0.0054, the study will be stopped as well. Already included patients will be followed
26 until the last follow-up moment.
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32 Sub-group analysis will be conducted by separately assessing patients with 1. colon and rectal
33 resections, 2. left and right sided resections, 3. malignant and benign pathology and 4. laparoscopic
34 and robotic-assisted surgery.
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40 **Data monitoring**

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

51 All adverse events related to indocyanine green will be reported. Furthermore, all events
52 that are serious adverse events will be registered in the online Dutch database,
53 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
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7 July 2020 in LUMC. Six centres are currently enrolling patients. Protocol amendments will
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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
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18 the first inclusion registered at clinicaltrials.gov (NCT04712032). A manuscript with the
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20 results of this study will be published in a peer-reviewed journal. Moreover, the results will
21
22 be shared via conference presentations.
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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 **FUNDING STATEMENT**

43
44 This research is funded by an Olympus Support Grant (2019-03-0077). The funder will have
45
46 no role in the conduct of the study; collection, management, analysis and interpretation of
47
48 the data; and decision to submit the manuscript for publication.
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53 **COMPETING INTERESTS STATEMENT**

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

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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, J. Sven D. Mieog, Jacobus Burggraaf, Alexander L. Vahrmeijer,
Denise E. Hilling

Participating investigators (in alphabetical order)

Tjeerd S. Aukema (HAGA hospital, The Hague, The Netherlands), Coen I.M. Baeten (Groene
Hart Hospital, Gouda, The Netherlands), Johanne G. Bloemen (Catharina Hospital,
Eindhoven, The Netherlands), Annelies Bodegom (Haaglanden Medical Center, The Hague,
The Netherlands), Fran Boersma (Leiden University Medical Center, Leiden, The
Netherlands), Koop Bosscha (Jeroen Bosch Hospital, Den Bosch, The Netherlands), Mark
A.M. Brouwers (HAGA hospital, The Hague, The Netherlands), Esther C.J. Consten (Meander
Medical Center, Amersfoort, The Netherlands), Pascal G. Doornebosch (IJsselland Hospital,
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

1
2
3 Wely (Bernhoven, Uden, The Netherlands), Lissa Wullaert (Amphia Hospital, The
4
5
6 Netherlands)
7
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13
14
15
16
17
18
19
20
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For peer review only

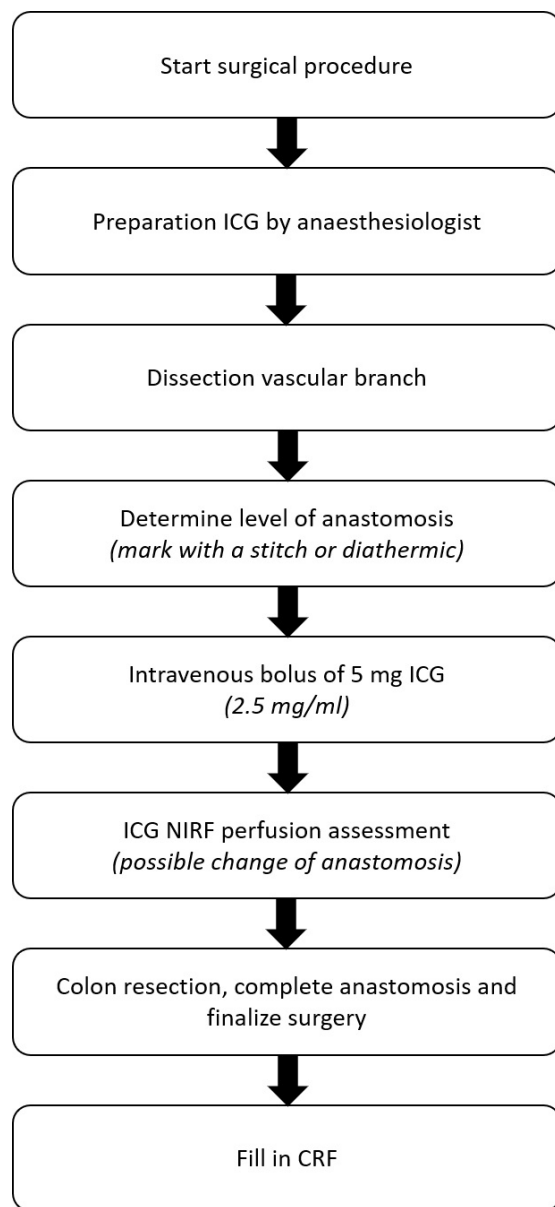


Figure 1 Surgical flowchart
ICG indocyanine green, NIRF Near-infrared, CRF case report form

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	
20			
21	contributorship		
22			
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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 rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-6
Objectives	#7	Specific objectives or hypotheses	5
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)	5-11
Methods:			
Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries	6

1		where data will be collected. Reference to where	
2			
3		list of study sites can be obtained	
4			
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			
12		surgeons, psychotherapists)	
13			
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15			
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			
33			
34			
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
42			
43			adhere to.
44			
45			
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47			
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			
59			
60			

1		change from baseline, final value, time to event),	
2		method of aggregation (eg, median, proportion),	
3		and time point for each outcome. Explanation of	
4		the clinical relevance of chosen efficacy and	
5		harm outcomes is strongly recommended	
6			
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12	Participant timeline	#13 Time schedule of enrolment, interventions	8
13		(including any run-ins and washouts),	
14		assessments, and visits for participants. A	
15		schematic diagram is highly recommended (see	
16		Figure)	
17			
18			
19			
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23			
24	Sample size	#14 Estimated number of participants needed to	10-11
25		achieve study objectives and how it was	
26		determined, including clinical and statistical	
27		assumptions supporting any sample size	
28		calculations	
29			
30			
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36			
37	Recruitment	#15 Strategies for achieving adequate participant	6
38		enrolment to reach target sample size	
39			
40			
41			
42	Methods:		
43			
44	Assignment of		
45	interventions (for		
46	controlled trials)		
47			
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52	Allocation:	#16a Method of generating the allocation sequence	8
53	sequence	(eg, computer-generated random numbers), and	
54	generation	list of any factors for stratification. To reduce	
55			
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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	8
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			
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25	Allocation:	#16c Who will generate the allocation sequence, who	6-8
26		will enrol participants, and who will assign	
27	implementation	participants to interventions	
28			
29			
30			
31			
32	Blinding (masking)	#17a Who will be blinded after assignment to	8
33		interventions (eg, trial participants, care	
34		providers, outcome assessors, data analysts),	
35		and how	
36			
37			
38			
39			
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41			
42	Blinding (masking):	#17b If blinded, circumstances under which unblinding	n/a surgeons are
43		is permissible, and procedure for revealing a	always unblinded
44	emergency	participant's allocated intervention during the trial	
45			
46	unblinding		
47			
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49			
50	Methods: Data		
51			
52	collection,		
53			
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				

1	analyses		subgroup and adjusted analyses)	
2				
3	Statistics: analysis	#20c	Definition of analysis population relating to	10-11
4	population and		protocol non-adherence (eg, as randomised	
5	missing data		analysis), and any statistical methods to handle	
6			missing data (eg, multiple imputation)	
7				
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13	Methods:			
14				
15	Monitoring			
16				
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18	Data monitoring:	#21a	Composition of data monitoring committee	n/a
19	formal committee		(DMC); summary of its role and reporting	
20			structure; statement of whether it is independent	
21			from the sponsor and competing interests; and	
22			reference to where further details about its	
23			charter can be found, if not in the protocol.	
24			Alternatively, an explanation of why a DMC is not	
25			needed	
26				
27				
28	Data monitoring:	#21b	Description of any interim analyses and stopping	11
29	interim analysis		guidelines, including who will have access to	
30			these interim results and make the final decision	
31			to terminate the trial	
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38	Harms	#22	Plans for collecting, assessing, reporting, and	11
39			managing solicited and spontaneously reported	
40			adverse events and other unintended effects of	
41			trial interventions or trial conduct	
42				
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48	Auditing	#23	Frequency and procedures for auditing trial	11
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1		conduct, if any, and whether the process will be	
2		independent from investigators and the sponsor	
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6	Ethics and		
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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			
15			
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)	
22			
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27			
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)	
31			
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35			
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	
40			
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43			
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	
47		before, during, and after the trial	
48			
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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	
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1		each study site	
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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			
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12			
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			
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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	
40			
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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			
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51	Appendices		
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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
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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](#) 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-051144.R2
Article Type:	Protocol
Date Submitted by the Author:	21-Jan-2022
Complete List of Authors:	Meijer, Ruben; Leiden University Medical Center; Centre for Human Drug Research Faber, Robin; Leiden University Medical Center Bijlstra, Okker; Leiden University Medical Center Braak, Jeffrey; Leiden University Medical Center Meershoek-Klein Kranenbarg, Elma; Leiden University Medical Center Putter, Hein; Leiden University Medical Center Mieog, J.; Leiden University Medical Center, Surgery Burggraaf, Koos; Centre for Human Drug Research, Vahrmeijer, Alexander; Leids Universitair Medisch Centrum, Surgery Hilling, Denise; Leiden University Medical Center; Erasmus Medical Center
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology, Oncology
Keywords:	SURGERY, Gastrointestinal imaging < RADIOLOGY & IMAGING, Gastrointestinal tumours < ONCOLOGY, Inflammatory bowel disease < GASTROENTEROLOGY

SCHOLARONE™
Manuscripts

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3 1 **AVOID; a Phase III, Randomised Controlled Trial Using Indocyanine Green for the Prevention**
4
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6 2 **of Anastomotic Leakage in Colorectal Surgery**

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8 3 Ruben P.J. Meijer^{1,2}, Robin A. Faber¹, Okker D. Bijlstra¹, Jeffrey P.B.M. Braak¹, Elma
9
10 4 Meershoek-Klein Kranenbarg¹, Hein Putter³, J. Sven D. Mieog¹, Koos Burggraaf², Alexander L.
11
12
13 5 Vahrmeijer¹, Denise E. Hilling^{1,4,*}, AVOID study group*

14
15
16
17
18 7 **Affiliations**

- 19
20 8 1. Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands
21
22 9 2. Centre for Human Drug Research, Leiden, the Netherlands
23
24
25 10 3. Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden,
26
27 11 the Netherlands
28
29 12 4. Department of Surgical Oncology and Gastrointestinal Surgery, Erasmus MC Cancer
30
31 13 Institute, University Medical Center Rotterdam, the Netherlands
32
33
34 14 * Members of the AVOID study group are listed in appendix A
35
36
37
38
39
40
41
42

43 17 ***Corresponding author**

44
45 18 D.E. Hilling, MD, PhD
46
47
48 19 Department of Surgery
49
50 20 Leiden University Medical Center
51
52 21 Leiden, The Netherlands
53
54
55 22 E-mail: d.hilling@erasmusmc.nl
56
57
58
59

60 24 **Word count: 2768**

1
2
3 **25 Abstract**
4

5
6 **26 Introduction:** Anastomotic leakage (AL) is one of the major complications after colorectal
7
8 **27** surgery. Compromised tissue perfusion at the anastomosis site increases the risk of AL.
9
10 **28** Several cohort studies have shown that indocyanine green (ICG) combined with fluorescent
11
12
13 **29** near-infrared imaging is a feasible and reproducible technique for real-time intraoperative
14
15 **30** imaging of tissue perfusion, leading to reduced leakage rates after colorectal resection.
16
17
18 **31** Unfortunately, these studies were not randomised. Therefore, we propose a randomised
19
20 **32** controlled trial to assess the value of ICG-guided surgery in reducing AL after colorectal
21
22
23 **33** surgery.

24
25 **34 Methods and analysis:** A multicentre, randomised controlled clinical trial will be conducted
26
27 **35** to assess the benefit of ICG-guided surgery in preventing AL. A total of 978 patients scheduled
28
29 **36** for colorectal surgery will be included. Patients will be randomised between the Fluorescence
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31 **37** Guided Bowel Anastomosis (FGBA) group and the Conventional Bowel Anastomosis (CBA)
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33 **38** group. The primary endpoint is clinically relevant AL (defined as requiring active therapeutic
34
35 **39** intervention or re-operation) within 90 days after surgery. Among the secondary endpoints
36
37 **40** are 30-day clinically relevant AL, all-cause postoperative complications, all-cause and AL
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39 **41** related mortality, surgical and non-surgical reinterventions, total surgical time, length of
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41 **42** hospital stay, and all-cause and AL related readmittance.
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45 **43 Ethics and dissemination:** This protocol has been approved by the Medical Ethical Committee
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47 **44** Leiden-Den Haag-Delft (METC-LDD) and is registered at ClinicalTrials.gov and trialregister.nl.
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49 **45** The results of this study will be reported through peer-reviewed publications and conference
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51 **46** presentations.
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55 **47 Trial registration numbers:** NCT04712032 and NL7502
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3 48 **Keywords:** bowel perfusion, near infrared fluorescence, indocyanine green, colorectal
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6 49 surgery, colorectal cancer, inflammatory bowel disease
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9 50 **Article Summary**

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11 51 **Strengths and limitations of this study**

- 12
13 52 1. This study is a multicentre randomised controlled trial
14 53 2. AL is a major complication with huge impact on patient's life
15 54 3. A clinically relevant endpoint will be used as the primary endpoint
16 55 4. Quantification of fluorescence-guided bowel perfusion with indocyanine green
17 56 would be a preferable addition, however its clinical correlation is unclear at this
18 57 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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3 81 invisible for the naked eye and will therefore not interfere with the surgical field.[27]
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6 82 Moreover, it is cleared quickly by the liver and has low toxicity.[28]
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9 83 Several cohort studies have investigated the benefit of NIR fluorescence imaging with ICG for
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11 84 intraoperative assessment of bowel perfusion. Some of these studies have shown that this
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13 85 technique enables clear visualisation of bowel perfusion within minutes after intravenous
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15 86 injection of ICG, resulting in reduced leakage rates and hospital stay.[29-32] Moreover,
16
17 87 several systematic reviews support this promising results concerning the prevention of AL [33
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19 88 34]. This has already led to the start of two randomised controlled trials (ICG-COLORAL;
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21 89 NCT03602677 and InTACT trial; ISCRN 13334746) which are currently recruiting patients. On the
22
23 90 other hand, Kin et al. have shown no benefit by using ICG in preventing AL.[35] Major
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25 91 drawbacks of these cohort studies are that they were not randomised and did not use
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27 92 clinically relevant AL as the primary endpoint. Therefore, we propose AVOID: '*Anastomotic*
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29 93 *leakage and Value Of Indocyanine green in Decreasing leakage rates*', a randomised
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31 94 controlled trial to investigate the benefit of intraoperative imaging with ICG for the reduction
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33 95 of AL rate in colorectal surgery.
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44 97 **METHODS AND ANALYSIS**

47 98 **Primary aim**

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50 99 The main objective of this study is to assess if ICG-guided perfusion assessment will result in
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52 100 a reduction of the AL rate within 90 days after surgery. ICG-guided perfusion assessment will
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54 101 be an adjunct to conventional laparoscopic imaging versus conventional laparoscopic
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56 102 imaging alone.
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3 103 **Hypothesis**
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6 104 It is hypothesised that intraoperative assessment of bowel perfusion using NIR fluorescence
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8 105 imaging with ICG will lower the incidence of clinically relevant AL within 90 days after
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10 106 colorectal resection.
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14 107 **Study design**
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17 108 In this multicentre randomised controlled trial, patients will be allocated to two groups: the
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19 109 Fluorescence Guided Bowel Anastomosis group (FGBA) or the Conventional Bowel
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21 110 Anastomosis group (CBA). Patients in the FGBA group will receive at least one dose of 5
22
23 111 milligram ICG, up to a maximum of 3 doses, to assess bowel perfusion. Patients in the CBA
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25 112 group will not receive any study related interventions and will be treated according to
26
27 113 standard of care. The allocated treatment result is not blinded for the surgeon performing
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29 114 the procedure. Patients will be unblinded after the procedure.
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35 115 **Setting**
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38 116 This national study will take place in multiple academic and large teaching hospitals in the
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40 117 Netherlands. More Dutch hospitals will be added during the course of the study.
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44 118 **Participants**
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47 119 All patients scheduled for laparoscopic or robotic-assisted colorectal surgery (malignant and
48
49 120 benign indications) with primary anastomosis will be screened for eligibility during
50
51 121 multidisciplinary team meetings and, when eligible for participation, informed about the
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53 122 study by their attending physician. It will be emphasized that a patient can withdraw from
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55 123 the study at any given moment without having to offer any reason. The fundamental
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3 124 concepts outlined in the Declaration of Helsinki will be followed during the execution of the
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6 125 trial.[36]
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9 126 **Sample size calculation**

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12 127 The power analysis was performed based on Dutch national AL percentages, derived from the
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14 128 Dutch ColoRectal Audit (DCRA).[37] It is hypothesized that the use of ICG will decrease the
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17 129 AL rate in colorectal surgery from 7 to 3%. With a significance of 0.0492 (adjusted for the
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19 130 interim analysis using the O'Brien-Flemming approach), power of 80%, drop-out of 5% and a
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22 131 control-intervention ratio of 1:1, a sample size of 978 (489:489) patients is needed.[38]
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25 132 **Inclusion criteria**

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28 133 In order to be eligible to participate in this study, a patient must meet all of the following
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30 134 criteria: aged 18 years and above, scheduled for laparoscopic or robotic-assisted colorectal
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33 135 resection with primary anastomosis, able to communicate in the Dutch language and willing
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35 136 to comply with the study restrictions, and signed informed consent prior to any study-
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38 137 mandated procedure.
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41 138 **Exclusion criteria**

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44 139 A potential patient who meets any of the following criteria will be excluded from
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46 140 participation in this study: known allergy or history of adverse reaction to ICG, iodine or
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49 141 iodine dyes, severe liver or kidney insufficiency, hyperthyroidism or a benign thyroid
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51 142 tumour, pregnant or breastfeeding women, scheduled for emergency surgery, palliative
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54 143 surgery or terminally ill, scheduled for a defunctioning stoma, taking phenobarbital,
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56 144 phenylbutazone, primidone, phenytoin, haloperidol, nitrofurantoin, and probenecid, or any
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59 145 other condition that the investigator considers to be potentially jeopardizing the patients
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3 146 well-being or the study objectives (following a detailed medical history and physical
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6 147 examination).
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8 9 148 **Randomisation**

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12 149 After inclusion in the study (i.e., after written informed consent is obtained), patients will be
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14 150 randomised to the FGBA or the CBA group. Randomisation will be performed online via
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16 151 Castor EDC (Castor, Amsterdam, the Netherlands) with variable block sizes and stratified by
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18 152 institute. The allocated treatment result is not blinded for the surgeon performing the
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20 153 procedure. Patients will be unblinded after the surgical procedure.
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24 25 154 **Intervention**

26
27 155 Patients in the CBA group will undergo laparoscopic or robotic colorectal resection
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29 156 according to standard of care using conventional methods to assess the integrity and
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31 157 viability of the anastomosis. Patients in the FGBA group will undergo the same standard of
32
33 158 care surgical procedure as patients in the CBA group; however, in addition to the
34
35 159 conventional methods, NIR fluorescence imaging with ICG will be performed to assess the
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37 160 bowel perfusion at the anastomosis side. All surgeries, in both arms, will be performed by
38
39 161 an attending surgeon. NIR fluorescence imaging with ICG will be performed as follows
40
41 162 (Figure 1): after dissection of the vascular branch, the preferred level of anastomoses
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43 163 (proximally and distally) will be highlighted by a stitch or diathermic mark in the adjacent
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45 164 mesocolon or mesorectum. Then, 5 mg ICG (2.5 mg/ml, Diagnostic Green, Aschheim,
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47 165 Germany), followed by 10 ml saline flush, will be injected intravenously by the
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49 166 anaesthesiologist. Within a few minutes, the anastomotic microvascularisation of both
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51 167 bowel ends will be assessed using the Olympus Medical Imaging Video System and
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53 168 Laparoscope (Olympus, Leiderdorp, the Netherlands) or Da Vinci Firefly (Intuitive Inc.,
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3 169 Sunnyvale, CA, United States of America). The green overlay setting of these systems will be
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6 170 used for perfusion assessment. The level of resection and subsequent anastomosis may be
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8 171 changed accordingly (with the mesocolic stitch serving as the baseline). During the
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11 172 procedure, the ICG injection (5 mg) may be repeated for a second or third time with a 15
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13 173 minute wash-out period between each administration. Repeated doses may be applicable
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15 174 when, for example, both anastomosis sides do not fit into the optical field, or when
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18 175 perfusion seems compromised after anastomosis finalisation. All injections, including the
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20 176 reason(s) for repeated injection(s), and the consequences of administration, will be
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22
23 177 documented in the case report form (CRF).

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26 178 The 90-day follow-up is a standard of care follow-up moment in all participating hospitals. It
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28 179 will be done either by phone, by videoconference or in person, according to standard of
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31 180 care in the participating hospital. Patients who, for any reason, do not visit the hospital 90
32
33 181 days after resection, will be contacted by phone and asked for any postoperative
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35 182 complications or reinterventions.

36 37 38 39 183 **Outcome measures**

40 41 42 184 *Primary outcome*

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44
45 185 The primary outcome is the rate of clinically relevant AL within 90 days after surgery. This
46
47 186 will be compared between the FGBA group using ICG for perfusion assessment and the
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49
50 187 standard of care surgery, CBA group. The definition of clinically relevant AL is derived from
51
52 188 the definition of Rahbari et al.[39] Grade B (requiring active therapeutic intervention but
53
54 189 manageable without re-operation) and C AL (requiring re-operation) will be considered
55
56
57 190 clinically relevant. There is no central study protocol for the detection of AL. No routine CT
58
59 191 scans will be performed for AL assessment. Post-operative blood tests, radiologic

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3 192 assessment and subsequent assessment of AL will be based on local protocols and the
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6 193 judgement of the local surgical team.
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9 194 *Secondary outcomes*

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12 195 1. 30-day clinically relevant AL
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14 196 2. 30- and 90-day all-cause postoperative complications
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17 197 3. 30- and 90-day mortality; all-cause and AL related
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19 198 4. 30- and 90-day reinterventions; surgical and non-surgical
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21
22 199 5. Total surgical time of primary surgery
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24 200 6. Postoperative length of hospital stay; primary stay and readmittance within 90 days
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26 201 7. Readmittance; all-cause and AL related
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32 203 **Training**

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35 204 Prior to their first inclusion, surgeons and other involved hospital staff of the participating
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37 205 center will be trained during a site initiation visit by the principal investigator or one of the
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40 206 coordinating investigators. If needed, training with the Olympus Medical Imaging Video
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42 207 System and Laparoscope or Da Vinci Firefly will be provided by either Olympus or Intuitive.
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44
45 208 Surgeons are invited to observe surgical procedures, using NIR fluorescence imaging with
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47 209 ICG for intraoperative assessment of bowel perfusion, in the LUMC. One of the coordinating
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50 210 investigators, with a broad experience in fluorescence-guided surgery, will assist all
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52 211 participating surgeons during their first number of cases to ensure standardization of the
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55 212 technique.
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3 213 This study is performed in collaboration with Olympus. In order to keep the study data as

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6 214 homogenous as possible, the use of camera system has been limited to the Olympus

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8 215 Medical Imaging Video System and the Da Vinci Firefly in case of robotic-assisted

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10 216 surgery.**Data collection**

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13 217 A CRF will be filled in during surgery by trained local research staff. This CRF captures

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15
16 218 baseline characteristics, basic surgical data and study specific data. For patients in the FGBA

17
18 219 group it will be documented whether the resection margins have been adjusted and, if so,

19
20 220 which margin (distal or proximal margin) and the extent of adjustment in centimetres. In

21
22 221 addition, in case of a non-planned defunctioning stoma, it will be recorded whether ICG-

23
24 222 guidance contributed to this decision. All clinical data will be prospectively registered via an

25
26 223 electronic CRF (eCRF) in a digital database of Castor EDC. We will not transfer or collect

27
28 224 imaging data (video or pictures) for postoperative analysis.

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33 225 **Data validation and management**

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36 226 Patient data will be registered coded and analysed by comparing the FGBA group with the

37
38 227 CBA group. Only the local investigators will have access to local source data after informed

39
40 228 consent is given. The research group from Leiden University Medical Centre (LUMC) will

41
42 229 have access to all coded data in the Castor EDC database.

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47 230 **Study timeline**

48
49 231 Patients have been included in the study from July 2020, starting in the LUMC. As per

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51 232 August 1st 2021, 352 patients were included in 6 different hospitals. With a mean inclusion

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53 233 rate of 40 patients per month the anticipated last inclusion will be in the final quarter of

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3 234 2022. There is no maximum for the number of centres nor the number of inclusions per
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5
6 235 centre.

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9 236 **Statistical analysis**

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12 237 The most recent version of SPSS (IBM, Armonk, New York, USA) will be used for statistical
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14 238 analysis. Categorical variables of the FGBA and CBA group will be compared by the Chi-
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16
17 239 Square test. Numerical variables will be compared by the independent sample T-test or the
18
19 240 Mann-Whitney U test, depending on distribution. All p-values will be 2-sided. A p-value of
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21 241 less than 0.0492 will indicate a statistically significant difference. All data will be analysed on
22
23
24 242 an intention-to-treat principle and, when applicable, on a per protocol analysis.

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26
27 243 The primary outcome measure, clinically relevant AL within 90 days after surgery, will be
28
29 244 compared using the Mantel-Haenszel test, stratified by centre.

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33 245 An interim analysis will be conducted after 489 patients have been randomised and reached
34
35 246 the last day of follow-up (day 90). This interim analysis will aim at stopping the study for
36
37 247 futility, if the conditional power for the primary endpoint (clinically relevant AL within 90
38
39 248 days after surgery) with the planned sample size, based on the observed results at the
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41 249 interim analysis, using the original settings of null and alternative hypothesis, is less than
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44
45 250 10%.

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48 251 If this interim analysis shows efficacy based on the primary endpoint with a nominal alpha
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50 252 level of 0.0054, the study will be stopped as well. Already included patients will be followed
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52
53 253 until the last follow-up moment.

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3 254 Sub-group analysis will be conducted by separately assessing patients with 1. colon and rectal
4
5 255 resections, 2. left and right sided resections, 3. malignant and benign pathology and 4. laparoscopic
6
7
8 256 and robotic-assisted surgery.
9

10 11 257 **Data monitoring** 12

13
14 258 The study will be monitored for quality and regulatory compliance, by study-independent
15
16 259 LUMC staff. Monitoring frequency will be at least annually, but may be increased depending
17
18
19 260 on findings.
20

21 22 261 **Adverse events** 23

24
25 262 All adverse events related to indocyanine green will be reported. Furthermore, all events
26
27 263 that are serious adverse events will be registered in the online Dutch database,
28
29
30 264 toetsingonline.nl, and in the eCRF of Castor EDC.
31

32 33 265 **Patient and Public Involvement** 34

35
36 266 Patients or public were neither involved in the development of the research questions and
37
38 267 outcome measures nor the planning of the study design. Patients are not involved in the
39
40
41 268 recruitment or conduct of the study. Results of the study will be published in peer-reviewed
42
43 269 journals, no other information of the results of the study are provided to the patients.
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45
46 270 Patients will not take part in assessment regarding possible burden of the interventions of
47
48 271 this study.
49

50 51 272 **EXPECTED LIMITATIONS AND DIFFICULTIES** 52

53
54 273 Intraoperative fluorescence assessment of bowel perfusion is currently a subjective tool.
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57 274 This will most likely influence our results as over 30 different surgeons will interpret the
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3 275 fluorescence output. Quantification of the NIR fluorescence signal would improve
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6 276 standardized assessment of tissue perfusion.
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9 277 Using different NIR platforms (the Olympus Medical Imaging Video System and
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11 278 Laparoscope, and the Da Vinci Firefly) will have some influence on our results as well.
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14 279 Nevertheless, both systems are optimized for the detection of ICG, we therefore think its
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16 280 effect on our study results is minimal.

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19 281 AL after colorectal surgery is a multifactorial complication. It is unclear which percentage of
20
21 282 AL is solely based on compromised perfusion. It is especially questionable if compromised
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24 283 perfusion plays a role in late AL (> 7 days after surgery).

25 26 27 284 **ETHICS AND DISSEMINATION**

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29
30 285 The study was approved by the certified Medical Ethics Review Committee Leiden, Den
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32 286 Haag, Delft (METC-LDD) on 11 November 2019 under identifier P19.079, and feasibility
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34 287 declarations as required by Dutch law, were obtained for the remaining hospitals. The
35
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37 288 protocol's current version (2.0) is dated 26 March 2020. The first patient was recruited on 2
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39
40 289 July 2020 in LUMC. Six centres are currently enrolling patients. Protocol amendments will
41
42
43 290 first be reviewed by the METC-LDD and after approval be shared with the participating
44
45 291 centres for local feasibility declarations.

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47
48 292 This study was prospectively registered at the Netherlands trial register (NL7502) and after
49
50 293 the first inclusion registered at clinicaltrials.gov (NCT04712032). A manuscript with the
51
52
53 294 results of this study will be published in a peer-reviewed journal. Moreover, the results will
54
55 295 be shared via conference presentations.

56 57 58 296 **AUTHOR CONTRIBUTIONS**

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2
3 297 RM, RF, OB, JB, EM, JM, KB, AV and DH all contributed to the study concept and design. HP
4
5
6 298 was responsible for the statistical analysis plan and the sample size calculation. RM, RF and
7
8 299 OB prepared the manuscript. JM, AV and DH supervised the manuscript preparation. All
9
10 300 authors and members of the AVOID study group reviewed the manuscript before
11
12
13 301 submission.

16 302 **FUNDING STATEMENT**

17
18
19 303 This research is funded by an Olympus Support Grant (2019-03-0077). The funder will have
20
21 304 no role in the conduct of the study; collection, management, analysis and interpretation of
22
23
24 305 the data; and decision to submit the manuscript for publication.

27 306 **COMPETING INTERESTS STATEMENT**

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29
30 307 AV and LS are members of the Diagnostic Green advisory board. All other authors declare to
31
32 308 have no competing interest concerning this work.

39 310 **FIGURE LEGENDS**

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41
42 311 Figure 1 Surgical flowchart

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44
45 312 ICG indocyanine green, NIRF Near-infrared, CRF case report form

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3 428 **List of members of the AVOID study group**
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6 429 **Academic committee**
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9 430 Ruben P.J. Meijer, Robin A. Faber, Okker D. Bijlstra, Jeffrey P.B.M. Braak, E. Meershoek-Klein
10
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12 431 Kranenbarg, Hein Putter, J. Sven D. Mieog, Jacobus Burggraaf, Alexander L. Vahrmeijer,
13
14

15 432 Denise E. Hilling
16

17 433 **Participating investigators** (in alphabetical order)
18
19

20 434 Tjeerd S. Aukema (HAGA hospital, The Hague, The Netherlands), Coen I.M. Baeten (Groene
21
22

23 435 Hart Hospital, Gouda, The Netherlands), Johanne G. Bloemen (Catharina Hospital,
24
25

26 436 Eindhoven, The Netherlands), Annelies Bodegom (Haaglanden Medical Center, The Hague,
27
28

29 437 The Netherlands), Fran Boersma (Leiden University Medical Center, Leiden, The
30
31

32 438 Netherlands), Koop Bosscha (Jeroen Bosch Hospital, Den Bosch, The Netherlands), Mark
33
34

35 439 A.M. Brouwers (HAGA hospital, The Hague, The Netherlands), Esther C.J. Consten (Meander
36
37

38 440 Medical Center, Amersfoort, The Netherlands), Pascal G. Doornebosch (IJsselland Hospital,
39
40

41 441 Capelle aan den IJssel, The Netherlands), Dashti Faraj (Groene Hart Hospital, Gouda, The
42
43

44 442 Netherlands), Paul D. Gobardhan (Amphia Hospital, The Netherlands), Fabian .A. Holman
45
46

47 443 (Leiden University Medical Center, Leiden, The Netherlands), Tessa Kauwenbergh (IJsselland
48
49

50 444 Hospital, Capelle aan den IJssel, The Netherlands), Andreas W.K.S. Marinelli (Haaglanden
51
52

53 445 Medical Center, The Hague, The Netherlands), Peter A. Neijenhuis (Alrijne Hospital,
54
55

56 446 Leiderdorp, The Netherlands), Koen C.M.J. Peeters (Leiden University Medical Center,
57
58

59 447 Leiden, The Netherlands), Daan J. Sikkenk (Meander Medical Center, Amersfoort, The
60
61

62 448 Netherlands), Laurents P.S. Stassen (Maastricht University Medical Center, Maastricht, The
63
64

65 449 Netherlands), Willem-Hans Steup (HAGA hospital, The Hague, The Netherlands), Maxime
66
67

68 450 J.M. van der Valk (IJsselland Hospital, Capelle aan den IJssel, The Netherlands), Bob J. van
69
70

1
2
3 451 Wely (Bernhoven, Uden, The Netherlands), Lissa Wullaert (Amphia Hospital, The
4
5
6 452 Netherlands)
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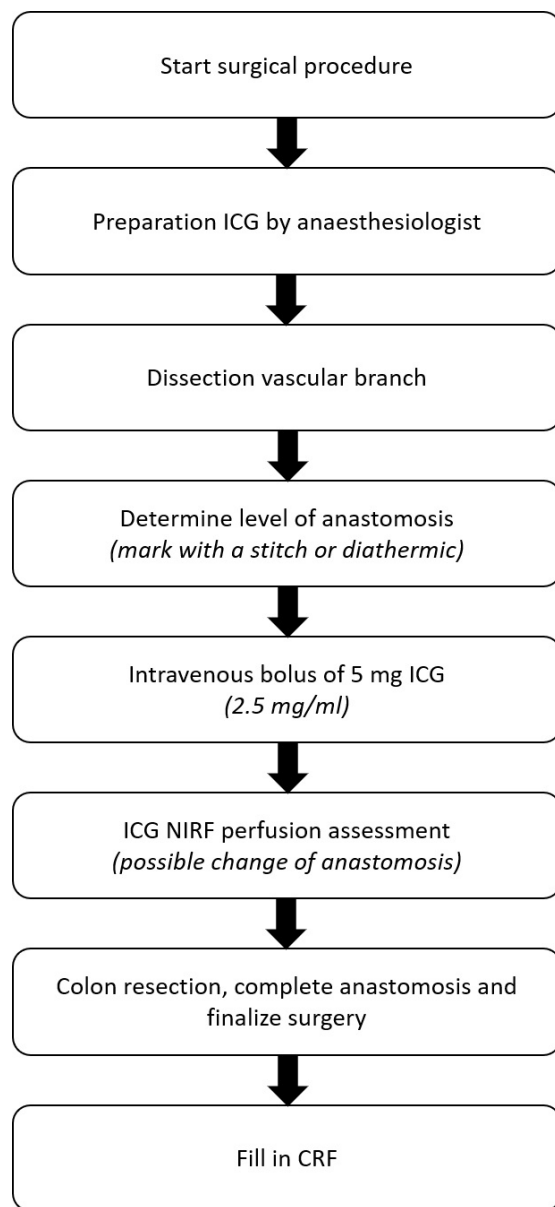


Figure 1 Surgical flowchart
ICG indocyanine green, NIRF Near-infrared, CRF case report form

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	
20			
21	contributorship		
22			
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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		
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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,	
38			
39	sponsor and funder	and interpretation of data; writing of the report;	
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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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groups overseeing the trial, if applicable (see
Item 21a for data monitoring committee)

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-6
Objectives	#7	Specific objectives or hypotheses	5
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)	5-11
Methods:			
Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries	6

1		where data will be collected. Reference to where	
2			
3		list of study sites can be obtained	
4			
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			
12		surgeons, psychotherapists)	
13			
14			
15			
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			
33			
34			
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
42			
43			adhere to.
44			
45			
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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			
59			
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1		change from baseline, final value, time to event),	
2		method of aggregation (eg, median, proportion),	
3		and time point for each outcome. Explanation of	
4		the clinical relevance of chosen efficacy and	
5		harm outcomes is strongly recommended	
6			
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12	Participant timeline	#13 Time schedule of enrolment, interventions	8
13		(including any run-ins and washouts),	
14		assessments, and visits for participants. A	
15		schematic diagram is highly recommended (see	
16		Figure)	
17			
18			
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24	Sample size	#14 Estimated number of participants needed to	10-11
25		achieve study objectives and how it was	
26		determined, including clinical and statistical	
27		assumptions supporting any sample size	
28		calculations	
29			
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37	Recruitment	#15 Strategies for achieving adequate participant	6
38		enrolment to reach target sample size	
39			
40			
41			
42	Methods:		
43			
44	Assignment of		
45	interventions (for		
46	controlled trials)		
47			
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52	Allocation:	#16a Method of generating the allocation sequence	8
53	sequence	(eg, computer-generated random numbers), and	
54	generation	list of any factors for stratification. To reduce	
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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	8
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			
21			
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24			
25	Allocation:	#16c Who will generate the allocation sequence, who	6-8
26		will enrol participants, and who will assign	
27	implementation	participants to interventions	
28			
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31			
32	Blinding (masking)	#17a Who will be blinded after assignment to	8
33		interventions (eg, trial participants, care	
34		providers, outcome assessors, data analysts),	
35		and how	
36			
37			
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42	Blinding (masking):	#17b If blinded, circumstances under which unblinding	n/a surgeons are
43		is permissible, and procedure for revealing a	always unblinded
44	emergency	participant's allocated intervention during the trial	
45			
46	unblinding		
47			
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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				
17	Data management	#19	Plans for data entry, coding, security, and	10-11
18			storage, including any related processes to	
19			promote data quality (eg, double data entry;	
20			range checks for data values). Reference to	
21			where details of data management procedures	
22			can be found, if not in the protocol	
23				
24				
25	Statistics: outcomes	#20a	Statistical methods for analysing primary and	10-11
26			secondary outcomes. Reference to where other	
27			details of the statistical analysis plan can be	
28			found, if not in the protocol	
29				
30				
31	Statistics: additional	#20b	Methods for any additional analyses (eg,	10-11
32				

1	analyses		subgroup and adjusted analyses)	
2				
3				
4	Statistics: analysis	#20c	Definition of analysis population relating to	10-11
5				
6	population and		protocol non-adherence (eg, as randomised	
7				
8	missing data		analysis), and any statistical methods to handle	
9				
10			missing data (eg, multiple imputation)	
11				
12				
13	Methods:			
14				
15	Monitoring			
16				
17				
18				
19	Data monitoring:	#21a	Composition of data monitoring committee	n/a
20				
21	formal committee		(DMC); summary of its role and reporting	
22				
23			structure; statement of whether it is independent	
24				
25			from the sponsor and competing interests; and	
26				
27			reference to where further details about its	
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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37				
38	Data monitoring:	#21b	Description of any interim analyses and stopping	11
39				
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	
45				
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48	Harms	#22	Plans for collecting, assessing, reporting, and	11
49				
50			managing solicited and spontaneously reported	
51				
52			adverse events and other unintended effects of	
53				
54			trial interventions or trial conduct	
55				
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58	Auditing	#23	Frequency and procedures for auditing trial	11
59				
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conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

11	Research ethics	#24	Plans for seeking research ethics committee /	12
12			institutional review board (REC / IRB) approval	
13	approval			
16	Protocol	#25	Plans for communicating important protocol	12
17	amendments		modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
29	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
36	6Consent or assent:	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
37	ancillary studies			
44	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
54	Declaration of	#28	Financial and other competing interests for principal investigators for the overall trial and	12-13
55	interests			

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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12			
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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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			
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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

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](#) in collaboration with [Penelope.ai](#)