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Near-infrared fluorescence cholangiography assisted laparoscopic cholecystectomy versus conventional laparoscopic cholecystectomy (FALCON trial): study protocol for a multicentre randomised controlled trial

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ABSTRACT

Introduction: Misidentification of the extrahepatic bile duct anatomy during laparoscopic cholecystectomy (LC) is the main cause of bile duct injury. Easier intraoperative recognition of the biliary anatomy may be accomplished by using near-infrared fluorescence (NIRF) imaging after an intravenous injection of indocyanine green (ICG). Promising results were reported for successful intraoperative identification of the extrahepatic bile ducts compared to conventional laparoscopic imaging. However, routine use of ICG fluorescence laparoscopy has not gained wide clinical acceptance yet due to a lack of high-quality clinical data. Therefore, this multicentre randomised clinical study was designed to assess the potential added value of the NIRF imaging technique during LC.

Methods and analysis: A multicentre, randomised controlled clinical trial will be carried out to assess the use of NIRF imaging in LC. In total, 308 patients scheduled for an elective LC will be included. These patients will be randomised into a NIRF imaging laparoscopic cholecystectomy (NIRF-LC) group and a conventional laparoscopic cholecystectomy (CLC) group. The primary end point is time to 'critical view of safety' (CVS). Secondary end points are 'time to identification of the cystic duct (CD), of the common bile duct, the transition of CD in the gallbladder and the transition of the cystic artery in the gallbladder, these all during dissection of CVS'; 'total surgical time'; 'intraoperative bile leakage from the gallbladder or cystic duct'; 'bile duct injury'; 'postoperative length of stay', 'complications due to the injected ICG'; 'conversion to open cholecystectomy'; 'postoperative complications (until 90 days postoperatively)' and 'cost-minimisation'.

Ethics and dissemination: The protocol has been approved by the Medical Ethical Committee of Maastricht University Medical Center/Maastricht University; the trial has been registered at ClinicalTrials.gov. The findings of this study will be disseminated widely through peer-reviewed publications and conference presentations.

Trial registration number: NCT02558556.

Strengths and limitations of this study

- This study is a multicentre, randomised, controlled trial.
- The study addresses a clinically important topic: safety of laparoscopic cholecystectomy.
- Operative end points will be assessed in a dual manner: peroperatively and also by an expert panel postoperatively based on video analysis.
- A more preferable primary end point would have been 'bile duct injury'; however, this is not achievable since very large sample sizes would be required for sufficient power.

INTRODUCTION

Laparoscopic cholecystectomy (LC) is the most commonly performed laparoscopic procedure in the Netherlands, with almost 23 000 procedures annually.[1] Bile duct injury during this procedure is rare with an incidence of 0.3–0.7%.[2–5] However, when bile duct injury or vascular injury is present, it results in significant clinical relevant morbidity and mortality, lower quality of life and extra costs.[6–10] Bile duct injury will generally lead to bile leakage and abdominal sepsis and can lead to bile duct obstruction with obstructive jaundice eventually leading to orthotropic liver transplantation or both.[7] Late recognition and management of bile duct injuries can lead to severe deterioration in the patient's condition, progressing to biliary peritonitis, sepsis, multiorgan failure and eventually death. Therefore, early recognition and treatment is important.[7 11] Misidentification of the extrahepatic bile duct anatomy during LC is the main cause of bile duct injury.[12]

To reduce this risk of bile duct injury, the critical view of safety (CVS) technique was introduced by Strasberg in 1995.[13] A recent Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) expert Delphi consensus deemed the CVS as being the most important factor for overall safety,[14] in accordance with the current Dutch Surgical Society Guideline for Laparoscopic Cholecystectomy.[15]

To establish CVS, two observation windows need to be created: one window between the cystic artery (CA), cystic duct (CD) and gallbladder and another between the CA, gallbladder and liver (see figure 1A,B). The CVS technique is especially aimed at mobilising the gallbladder neck from the liver, in order to obtain a circumferential identification of the transition of the CD into the gallbladder. Nowadays, the CVS technique is the gold standard to perform a safe cholecystectomy with identification of the vital structures such as the CD.[16–20] According to a Dutch nationwide survey in 2011, 97.6% of the Dutch surgeons use the CVS technique.[21] However, according to a recent study by Nijssen *et al*,[22] only in 10% of the laparoscopic cholecystectomies CVS is actually established. This could mean that it is more difficult to establish CVS than thought before, thus resulting in more bile duct injury than necessary.

Nowadays, there are several imaging techniques, such as intraoperative cholangiography (IOC) and near-infrared fluorescence (NIRF) imaging, to identify the relevant anatomical structures easier. IOC has been advised to reduce the risk of bile duct injury.[2 16 23] However, this radiological imaging of the biliary tree is not adopted worldwide in standard LC, as the procedure takes time, involves radiation exposure and requires additional equipment and manpower. Moreover, the interpretation of an intraoperative cholangiogram with potentially distorted anatomy clearly depends on the expertise of the surgeon. Therefore, worldwide consensus about implementation of IOC is still lacking.[24]

NIRF imaging after intravenous injection of indocyanine green (ICG) is a promising new technique for easier intraoperative recognition of the biliary anatomy.[25 26] ICG is cleared quickly and exclusively by the liver after intravenous administration and has a very well-known pharmacokinetic and safety profile. Neither radiological support nor additional intervention such as opening the cystic or common bile duct (CBD) is required, making it an easy, real-time and flexible technique to use during surgery. By real-time identification of the vital structures being the CD and CBD within the already adapted CVS technique, it may improve the outcome of LC.[16 27 28] NIRF imaging using ICG has been evaluated in various animal models[29–31] and in open, laparoscopic and single-incision laparoscopic cholecystectomies.[30 32–34] Promising results were presented for safe and successful intraoperative

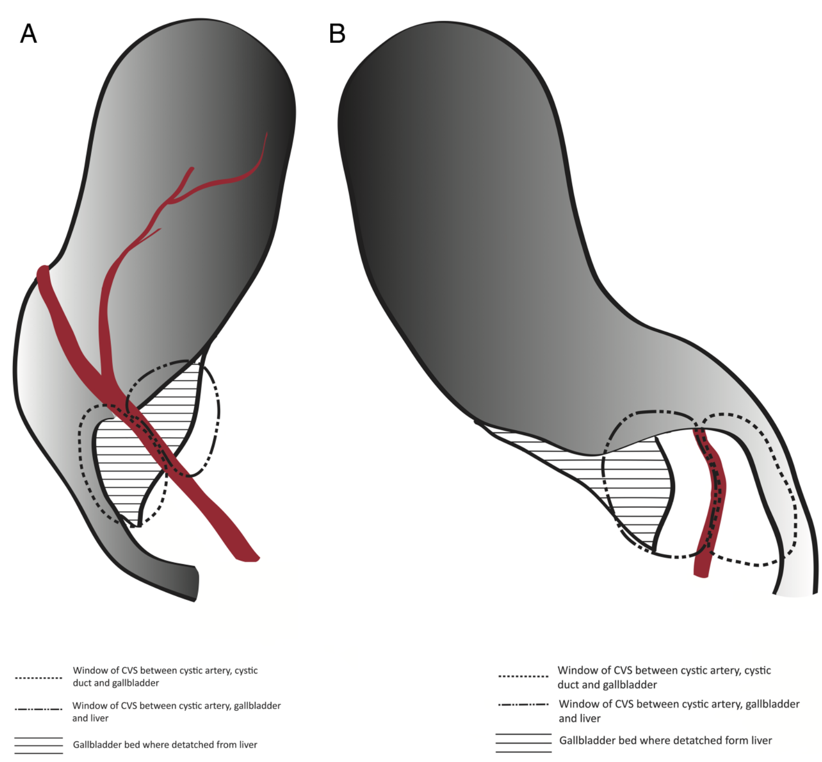


Figure 1 (A) CVS anterior view and (B) CVS posterior view. Two windows are created. One window between the cystic artery, cystic duct and gallbladder, the other between the CA, gallbladder and liver. CA, cystic artery; CVS, critical view of safety.

identification of the CBD and the CD, compared to conventional laparoscopic imaging. Furthermore, a clinical study (n=30) showed that the NIRF imaging technique provided significantly earlier identification of the extrahepatic bile ducts during the CVS dissection phase: up to 10 min earlier identification of the CD and CBD could be obtained.[35] Real-time imaging of the hepatic and cystic arteries was also achieved when a repeated dose of ICG was given.[35–37]

Despite these encouraging results derived from clinical feasibility studies, the routine use of ICG fluorescence laparoscopy has not gained wide clinical acceptance yet due to a lack of high-quality clinical data. Therefore, a multicentre randomised clinical study was designed to assess the added value of the NIRF imaging technique during LC. The ultimate goal of this technique is to perform a safer procedure leading to a reduction in vascular and bile duct injuries. The primary objective of the present study is to evaluate whether earlier establishment of CVS can be obtained using the NIRF imaging technique during LC.

METHODS AND ANALYSIS

Primary aim

The main objective of the study is to evaluate whether earlier establishment of the CVS can be obtained using the NIRF imaging technique during elective LC, by applying NIRF imaging as an adjunct to conventional laparoscopic imaging versus conventional laparoscopic imaging alone.

Hypothesis

It is hypothesised that standard application of NIRF imaging during LC will result in establishment of CVS at least 5 min earlier and with more certainty regarding visualisation of biliary anatomy when compared to conventional laparoscopic imaging alone.

Study design

This multicentre randomised controlled clinical trial includes two randomisation arms: a NIRF-LC (laparoscopic cholecystectomy) group—this group of patients will undergo NIRF cholangiography assisted laparoscopic cholecystectomy and a conventional laparoscopic cholecystectomy (CLC) control group—this group will undergo CLC.

Setting

This study will initially take place in five large teaching hospitals in the Netherlands, of which three are Academic Medical Centers. After the study in these centres has started, international centres will be included.

Participants

In the FALCON trial, a total of 308 patients will be included at the Departments of Surgery of the participating centres. The centres will be supported by the trial coordinator (JvdB) and by the Clinical Trial Center Maastricht (CTCM) (see also under the 'data monitoring' section). Further, no additional strategies for achieving adequate participant enrolment to reach the target sample size are considered necessary, as LC is a commonly performed surgery.

Sample size calculation

The number of 308 participants is based on pilot data,[35 38] where the identification of the CD and CBD was established, respectively, 11 and 10 min earlier using fluorescence laparoscopic imaging compared to conventional laparoscopic imaging. A sample size of 131 for each randomisation arm has been calculated to detect a reduction in 'time to establishment of CVS' of at least 5 min with a power of 80% and an α of 0.05 (95% CI). Assuming a withdrawal rate of 15% (due to usual reasons for dropout in combination with technical difficulties concerning the video recordings) during the trial, we will require a total of 308 ($n=2\times131+15\%$).

All patients (age >18 years) scheduled for an elective LC and meeting the inclusion criteria will be suitable for inclusion.

Inclusion criteria

The inclusion criteria are as follows: male and female patients, aged 18 years and above, scheduled for elective LC, with normal liver and renal function, no hypersensitivity for iodine or ICG, able to understand the nature of the study procedures, willing to participate and give written informed consent and Physical Status Classification of ASA I/ASA II.

Exclusion criteria

The exclusion criteria are as follows: age <18 years, liver or renal insufficiency, known iodine or ICG hypersensitivity, pregnancy or breastfeeding, not able to understand the nature of the study procedure and a Physical Status Classification of ASA III and above.

Participants can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a participant from the study for urgent medical reasons. Conversion to open cholecystectomy, before CVS is established, is a reason for study withdrawal. Furthermore, if the video recordings of the laparoscopic procedure were not successful, the procedure will be unsuitable for analysis of all predefined end points. There are no other specific criteria for withdrawal. In case of withdrawal, participants will be replaced to achieve the calculated sample size. All inclusions will be analysed on an intention-to-treat basis.

Randomisation

All included patients will be randomised centrally using block randomisation with sealed envelopes and stratification per participating centre. After signing the informed consent form, the next sealed envelope in line will be opened by the coordinating investigator. There will be no blinding of patients or surgeons.

Intervention

The CLC group will undergo conventional laparoscopic cholecystectomy. The NIRF-LC group will undergo near-infrared fluorescence cholangiography using a laparoscopic NIRF imaging system (Karl Storz GmbH, Tuttlingen, Germany). To obtain fluorescence imaging of the biliary tract and CA, a NIRF contrast agent will be administered. Directly after the induction of anaesthesia, 2.5 mg of ICG (2.5 mg/mL; Diagnostic Green, Aschheim, Germany) will be given intravenously. A repeat injection of 2.5 mg will be administered for concomitant arterial and biliary fluorescence delineation after achievement of CVS.

Outcome measures

The primary outcome measure is time to identification of CVS. This end point is used as a surrogate for bile duct identification without surgical exploration. CVS is established if the following three criteria are met:

1. Mobilisation of the gallbladder infundibulum for one-third of the length of the gallbladder from the liver bed.
2. Circumferential exposure of the CD and confirmation of its transition in the gallbladder.
3. Circumferential exposure of the CA and confirmation of its transition in the gallbladder.

Secondary outcome measures are listed in table 1.

Data collection

Intraoperatively, a case report form will be filled in. A structure is scored as 'identified' if its localisation is confirmed with great certainty by the experienced surgeon. The attending surgeon will be consulted to decide whether he believes CVS is established.

In accordance with regular care, all laparoscopic surgical procedures will be digitally recorded. An expert panel, consisting of three highly experienced laparoscopic surgeons, will analyse the data using video

Table 1 Secondary outcome measures

Outcome measure	Definition
Time until identification of the CD	Time in minutes
Time until identification of CBD	Time in minutes
Time until identification of the transition of CD into the gallbladder	Time in minutes
Time until identification of the transition of the CA into the gallbladder	Time in minutes
Total surgical time	Time in minutes from skin incision to the end of skin closure
Visualisation of CVS and visualisation of the transition of the CD and CA into the gallbladder	Time in minutes
Intraoperative bile leakage from the gallbladder or CD	Visualised bile leakage or spill during surgery
Bile duct injury	Any injury to the main biliary tree; will be classified using the Strasberg Classification System[13] Type A: injury to the CD or from minor hepatic ducts draining the liver bed Type B: occlusion of biliary tree, commonly aberrant right hepatic duct(s) Type C: transection without ligation of aberrant right hepatic duct(s) Type D: lateral injury to a major bile duct Type E:[1–5] injury to the main hepatic duct; classified according to level of injury
Postoperative length of hospital stay	Duration from date of admission (included) to date of discharge (included)
Complications due to injected contrast agent	Any complication potentially caused by injected ICG
Conversion to open cholecystectomy	Laparoscopic approach converted to an open operation, or in which an abdominal incision to assist the procedure was needed
90-day all-cause postoperative complications	Any complication, up to 90 days, described by the Clavien-Dindo classification of postoperative complications.[39] Specific attention to bile leak, CBD injury, wound infection, intra-abdominal collection, pancreatitis, CBD stones, ICU/HDU readmissions; prospectively assessed during admission; thereafter immediately to be reported to study coordinator
Cost minimisation	Difference in costs (in Euros) between conventional LC and NIRF-LC

CA, cystic artery; CBD, common bile duct; CD, cystic duct; CVS, critical view of safety; LC, laparoscopic cholecystectomy; NIRF, near-infrared fluorescence.

recordings: time until identification of the CD and of its transition into the gallbladder; time until identification of the CA and its transition into the gallbladder during dissection of CVS and when and whether CVS is established. Eventually, all five observers (the surgeon or surgical trainee, PhD researcher or local researcher during the operation and the three postoperative observers) will individually assess the above-mentioned end points. The mean values of these five assessments will be used for each of the end points. All clinical data are prospectively registered in a database.

OsiriX V.5.5.1. Imaging Software (Prixmeo, Geneva, Switzerland) will be used for objective assessment of the degree of fluorescence illumination in the extrahepatic bile ducts. The fluorescence images will be analysed by determining the target-to-background ratio (TBR). TBR is defined as the mean fluorescence intensity (FI) of two point regions of interest (ROIs) in the target (ie, CBD, CD or CA) minus the mean FI of two background (BG) ROIs in the liver hilum, divided by the mean FI of the two background ROIs in the liver hilum; that is TBR=(FI of target−FI of BG)/FI of BG.

The costs made in the two groups will be compared, resulting in a cost-minimisation analysis. This analysis will include the costs made by using the operation theatre in terms of fluorescence laparoscopy equipment, the fluorescent dye ICG, morbidity, mortality and postoperative hospital stay.

In figure 2, a flow chart of the study procedure for the NIRF-LC group and the CLC-group is presented.

Data validation and management

Patient data will be anonymously registered and analysed by comparing NIRF-LC with CLC. Only the investigators will have access to the patient data after informed consent is given.

Study timeline

In figure 3, the study timeline is presented. From January 2016 until January 2018, data will be collected; in September 2016, March 2017, September 2017 and March 2018, the expert panel will evaluate the video material for end points; around July 2018, data analysis is expected to be complete.

Participants will be informed about the study during their preoperative visit to the outpatient clinic. Thereafter, patients have at least a week to consider participation in the study. During their elective surgery, the near-infrared fluorescence laparoscopy will be used if the patient is randomised in the NIRF-LC group. After surgery, a 90-day follow-up period follows, and then possible complications will be evaluated.

Statistical analysis

For statistical analysis, the most recent version of SPSS (IBM, Armonk, New York, USA) will be used. Baseline characteristics such as patient clinical history (including previous surgery), age, body mass index and indication for the procedure will be recorded and compared between the intervention (NIRF-LC) and control groups (CLC). Categorical baseline variables will be compared using a χ^2 test, while numerical variables will be compared by the independent sample t-test or the Mann-Whitney U test, depending on the distribution.

The primary outcome measure, namely, time until establishment of CVS, will be given in minutes, with a mean and SD. A linear regression analysis will be applied for determination of possible significant differences between the time measurements, therewith comparing the NIRF-LC group to the CLC group. This will be conducted to determine whether a reduction in time can in fact be achieved using the NIRF imaging technique compared to CLC.

All numerical secondary outcomes such as time until visualisation of CD and CA will be analysed using a linear regression model. In case of missing values, a Cox regression analysis will be performed. Missing values can occur especially in the postoperative analysis by the expert panel, when the panel concludes that, contrary to the opinion of the operating team, actually no CVS was obtained or that the transition of the CD or CA in the gallbladder had actually not been properly identified. All categorical secondary outcomes such as bile duct injury and conversion to open surgery will be analysed with a logistic regression model.

Data monitoring

An independent data monitoring committee will monitor the study procedures and data management. This team consists of independent and certified persons from the CTCM. No interim analysis will be performed. Adverse events and serious adverse events will be centrally reported in the online database, toetsingonline.nl.

ETHICS AND DISSEMINATION

The proposed study is approved by the Medical Ethics committee of Maastricht University Medical Center/Maastricht University. Possible protocol amendments will be sent to the Medical Ethics Committee of Maastricht University Medical Center/Maastricht University. After approval, the changes will be communicated on clinicaltrials.gov and to the relevant parties.

Is there scientific and clinical value in conducting this study?

Despite the promising results from previous feasibility studies, a lack of solid clinical data precludes wide clinical acceptance of the routine use of ICG fluorescence laparoscopy. This multicentre randomised clinical study can provide such data.

Risk–benefit assessment

There are no additional risks accompanied by the laparoscopic NIRF imaging systems, compared to conventional laparoscopic imaging. The gifts of ICG are the

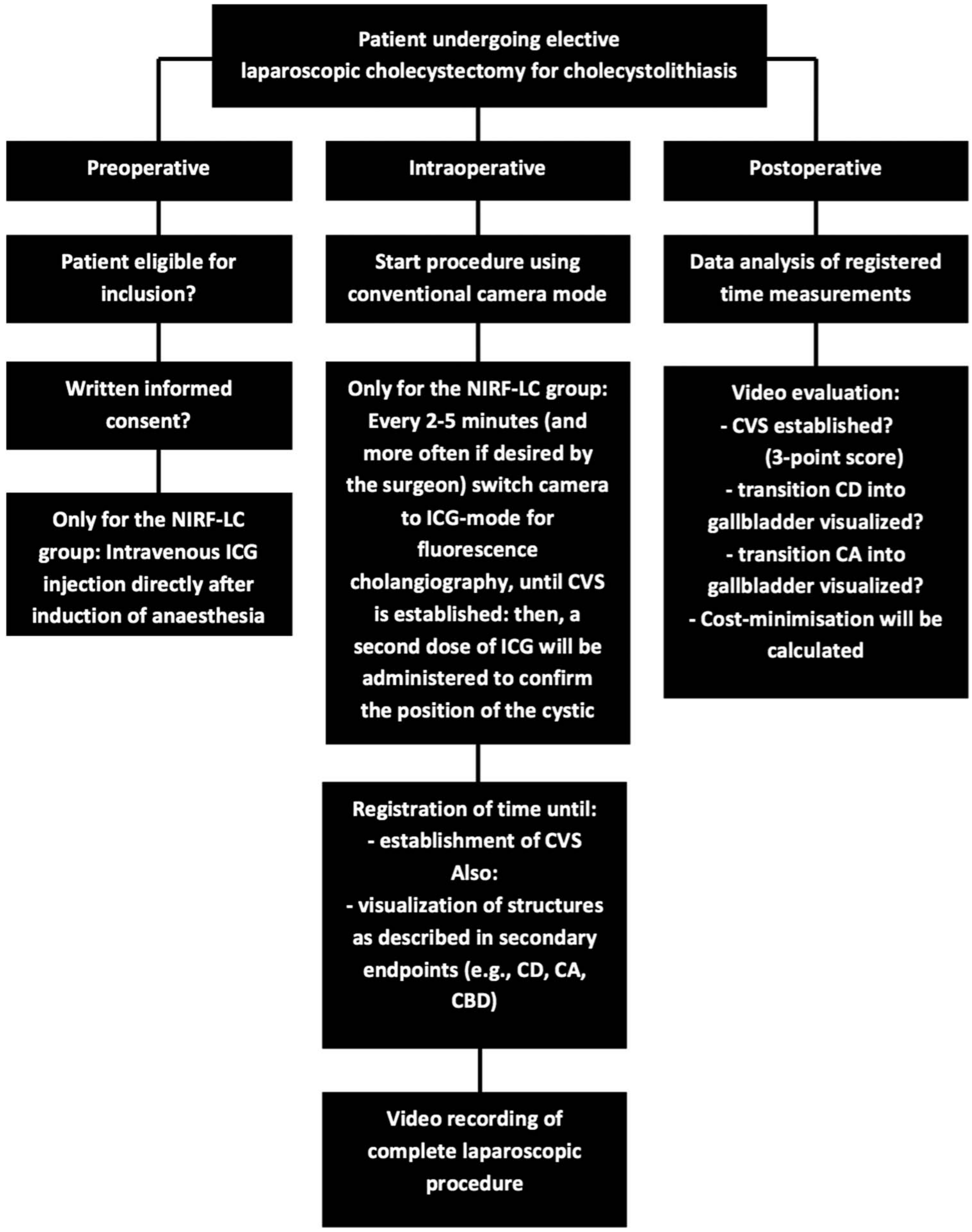
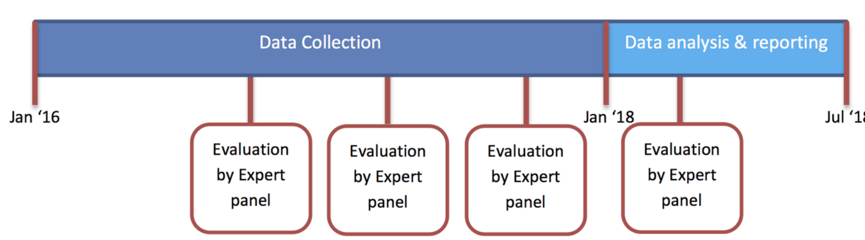


Figure 2 Flow chart of study procedures. CA, cystic artery; CD, cystic duct; CVS, critical view of safety; ICG, indocyanine green.

Figure 3 Study timeline.



only additional (minimally) invasive interventions for the patient. ICG preparations can, in very rare cases, cause nausea and anaphylactoid or anaphylactic reactions (<1:10 000). Patients with terminal renal insufficiency seem to be more prone for such an anaphylactic reaction. Estimated death due to anaphylaxis is reported as <1 per 330 000.[40–43] Symptoms include anxiety, feeling of warmth, pruritus, urticaria, acceleration of heart rate, decrease in blood pressure, shortness of breath, bronchospasm, flushing, cardiac arrest, laryngospasm, facial oedema and nausea. Together with the anaphylactoid reaction, hypereosinophilia may occur. If, contrary to expectations, symptoms of anaphylaxis occur, the following measures will be taken: stop further administration of ICG, leave injection catheter or cannula in the vein, keep airways free, inject 100–300 mg hydrocortisone or a similar preparation by rapid intravenous injection, substitute volume with isotonic electrolyte solution, give oxygen and monitor the circulation and slowly administer antihistamines intravenously. In case of an anaphylactic shock, the patient will be placed in the recumbent position with legs raised, volume will be rapidly substituted with, for example, isotonic electrolyte solution (pressure infusion), plasma expanders. Furthermore, 0.1–0.5 mg epinephrine will be administered and immediately diluted to 10 mL with 0.9% saline intravenously. If necessary, this will be repeated after 10 min.

The benefit for the patients in the NIRF-LC group will possibly include a shorter period to the establishment of CVS and the clearer identification of CVS and its anatomical components.

Do the individuals give informed consent?

To each patient, that is, a potential candidate for inclusion, thorough patient information will be given. From each individual who is willing to participate, written informed consent will be obtained by one of the investigators. The ethical issues of the trial will be thoroughly explained and discussed, verbally and in writing. The basic principles laid down in the Declaration of Helsinki[44] will be followed throughout the execution of the trial. Accordingly, each participant has the right to withdraw from the study at any given moment without having to explain this decision in any way.

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Disclaimer The funders will not have authority over any of the study-related activities, including data collection, data management, analysis, interpretation of data, writing the report or submission for publication.

Competing interests None declared.

Ethics approval Ethics approval was given by the Medical Ethical Committee, Maastricht University Medical Center/University of Maastricht.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement This is a research protocol. That means that the data for this study are being retrieved at this moment. All authors have access to these data, and these data will be published as described in the protocol, coordinated by JvdB.

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