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Near-infrared Fluorescence Cholangiography assisted Laparoscopic Cholecystectomy versus Conventional Laparoscopic Cholecystectomy (FALCON trial): study protocol for a multicenter randomized controlled trial.

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Trial registration

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ABSTRACT

Introduction:

Misidentification of the extra-hepatic bile duct anatomy during laparoscopic cholecystectomy 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 intravenous injection of indocyanine green (ICG). Promising results were reported for successful intraoperative identification of the extra-hepatic 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 multicenter randomized clinical study was designed to assess the potential added value of the NIRF-imaging technique during laparoscopic cholecystectomy.

Methods and Analysis:

A multi-center, randomized controlled clinical trial will be carried out to assess the use of NIRF imaging in laparoscopic cholecystectomy. In total 308 patients scheduled for an elective laparoscopic cholecystectomy for gallstone disease will be included. These patients will be randomized into a NIRF-imaging laparoscopic cholecystectomy (NIRF-LC) group and conventional laparoscopic cholecystectomy (CLC) group. The primary endpoint is time to 'Critical View of Safety' (CVS). Secondary endpoints 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-minimization".

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.

Keywords

Near-Infrared Fluorescence Imaging (NIRF), Indocyanine Green (ICG), Laparoscopic Cholecystectomy (LC), Critical View of Safety (CVS)

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, multi-organ failure and eventually death. Therefore, early recognition and treatment is important (7, 11). Misidentification of the extra-hepatic bile duct anatomy during laparoscopic cholecystectomy 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 Critical View of Safety 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, cystic duct and gallbladder, another between the cystic artery, gallbladder and liver (see figure 1a and 1b). The CVS technique is especially aimed at mobilizing the gallbladder neck from the liver, in order to obtain a circumferential identification of the transition of the cystic duct (CD) into the gallbladder. The CVS technique is the gold standard nowadays 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, only in 10% of the laparoscopic cholecystectomies CVS is actually established (22). 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 to identify the relevant anatomical structures easier, such as intraoperative cholangiography (IOC) and near-infrared fluorescence (NIRF) imaging. 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 laparoscopic cholecystectomy, as the procedure takes time, radiation exposure is involved and additional equipment and manpower for the procedure are required. 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 intraoperative cholangiography is still lacking (24).

Near-infrared fluorescence (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 is required, making it an easy, real-time and flexible technique to use technique during surgery. By real-time identification of the vital structures being the cystic duct and common bile duct within the already adapted CVS technique, it may improve the outcome of laparoscopic cholecystectomy (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 identification of the common bile duct and the cystic duct, compared to conventional laparoscopic imaging. Furthermore, a clinical study (n=30) showed that the NIRF imaging technique provided significantly earlier identification of the extra-hepatic bile ducts during the CVS dissection phase: up to 10 minutes earlier identification of the cystic duct and common bile duct could be obtained (35). Real-time imaging of the hepatic and cystic arteries was also achieved when given 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 multicenter randomized clinical study was designed to assess the added value of the NIRF imaging technique during laparoscopic cholecystectomy. 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 Critical View of Safety can be obtained using the NIRF imaging technique during laparoscopic cholecystectomy.

METHODS AND ANALYSIS

Primary aim: The main objective of the study is to evaluate whether earlier establishment of the Critical View of Safety can be obtained using the NIRF imaging technique during elective laparoscopic cholecystectomy for symptomatic bile stone disease, by applying NIRF imaging as an adjunct to conventional laparoscopic imaging versus conventional laparoscopic imaging alone.

Hypothesis: It is hypothesized that standard application of NIRF imaging during laparoscopic cholecystectomy will result in establishment of Critical View of Safety at least 5 minutes earlier and with more certainty regarding visualization of biliary anatomy when compared to conventional laparoscopic imaging alone.

Study design: A multicenter randomized controlled clinical trial, with two randomization arms: a NIRF-LC (laparoscopic cholecystectomy) group: this group of patients will undergo NIRF cholangiography assisted laparoscopic cholecystectomy; a CLC (conventional laparoscopic cholecystectomy) control group: this group will undergo conventional laparoscopic cholecystectomy.

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 centers has started, international centers will be included.

Participants: In the FALCON trial, a total of 308 patients will be included at the Departments of Surgery of the participating centers.

Sample size calculation: The number of 308 participants is based on pilot data (35, 38) in which identification of the cystic duct and common bile duct was established respectively 11 and 10 minutes earlier using fluorescence laparoscopic imaging compared to conventional laparoscopic imaging. A sample size of 131 for each randomization arm has been calculated to detect a reduction in 'time to establishment of CVS' of at least 5 minutes with a power of 80% and an α of 0.05 (95%-confidence). Assuming a withdrawal rate of 15% (due to usual reasons for drop-out in combination with technical difficulties concerning the video recordings) during the trial, a total of 308 (n = 2 x 131 + 15%) will be required

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

Inclusion criteria: Male and female patients, aged 18 years and above, scheduled for elective laparoscopic cholecystectomy, with uncomplicated symptomatic cholecystolithiasis as the indication for surgery, 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, Physical Status Classification of ASA I / ASA II.

Exclusion criteria: Age < 18 years, acute or chronic cholecystitis as indication for surgery, cholecystectomy after biliary pancreatitis, suspected malignancy, 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.
Subjects 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 subject 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 endpoints. There are no other specific criteria for withdrawal. In case of withdrawal, individual subjects will be replaced to achieve the calculated sample size. All inclusions will be analyzed on an intention-to-treat basis.

Randomization: All included patients will be randomized centrally using block randomization with sealed envelopes and stratification per participating center. 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 (CLC). 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 cystic artery a NIRF contrast agent will administered. Directly after induction of anesthesia 2,5 mg of Indocyanine Green (ICG) (2.5mg/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 endpoint is used as a surrogate for bile duct identification without surgical exploration. CVS is established if the following three criteria are met:

1. Mobilization of the gallbladder infundibulum for 1/3rd of the length of the gallbladder from the liver bed
2. Circumferential exposure of the cystic duct and confirmation of its transition in the gallbladder
3. Circumferential exposure of the cystic artery and confirmation of its transition in the gallbladder

Secondary outcome measures are listed in table 1:

Table1: Secondary outcome measures

Outcome measure	**Definition**
Time until identification of the cystic duct (CD)	Time in minutes
Time until identification of common bile duct	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 cystic artery (CA) into the gallbladder	Time in minutes
Total Surgical time	Time in minutes from skin incision to the end of skin closure
Visualization of CVS and visualization of the transition of the cystic duct and cystic artery into the gallbladder	Time in minutes
Intraoperative bile leakage from the gallbladder or cystic duct	Visualized 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 cystic duct 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 Minimization	Difference in costs (in Euros) between conventional LC and NIRF LC

Data collection: Intra-operatively a Case Report Form will be filled in. A structure is scored as 'identified' if its localization 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 analyze the data using video recordings: time until identification of the cystic duct and of its transition into the gallbladder; time until identification of the cystic artery and its transition into the gallbladder during dissection of CVS; 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 endpoints. Mean values of these five assessments will be used for each of the endpoints. All clinical data are prospectively registered in a database.

OsiriX 5.5.1. Imaging Software (Prixmeo, Geneva, Switzerland) will be used for objective assessment of the degree of fluorescence illumination in the extra-hepatic bile ducts. The fluorescence images will be analyzed by determining target-to-background ratio (TBR). TBR is defined as the mean fluorescence intensity (FI) of two point regions of interest (ROIs) in the target (i.e. CBD, CD or CA) minus the mean fluorescence intensity of two background (BG) ROIs in the liver hilum, divided by the

mean fluorescence intensity of the two background ROIs in the liver hilum; in formula: TBR = (FI of target – FI of BG) / FI of BG.

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

In figure 2a and 2b, a flowchart of the study procedure for both the NIRF-LC group and the C group is presented.

Data validation and management: Patient data will be anonymously registered and analyzed 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 endpoints; 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 randomized in the NIRF-LC group. After surgery a 90day follow-up period follows after which possible complications will be evaluated.

Statistical analysis: For statistical analysis, the most recent version of SPSS (IBM, Armonk, NY, USA) will be used. Baseline characteristics such as patient clinical history (including previous surgery), age, Body Mass Index, 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 Chi-Square 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 standard deviation. 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 NIRF imaging technique compared to CLC.

All numerical secondary outcomes such as time until visualization of cystic duct and cystic artery will be analyzed 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 cystic duct or cystic artery 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 analyzed with a logistic regression model.

Data monitoring: An independent data monitoring committee will monitor the study procedures and data management. 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 send to the Medical Ethics committee of Maastricht University Medical Center / Maastricht University. After approval the changes will be communicated in the registration on clinicaltrials.gov and to the for the amendment relevant parties.

1. 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 multicenter randomized clinical study can provide such data.

2. 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 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 less than 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 edema, 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, slowly administer antihistamines intravenously. In case of an anaphylactic shock, the patient will be placed in recumbent position with legs raised, volume will be rapidly substituted with e.g. isotonic electrolyte solution (pressure infusion), plasma expanders. And 0.1-0.5 mg adrenaline will be administered immediately diluted to 10 ml with 0.9% saline intravenously. If necessary, this will be repeated after 10 minutes

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

3. Do the individuals give informed consent?

To each patient that is a potential candidate for inclusion thorough patient inflation will be given. From each subject that 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, both 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.

Contributors: JvbB, RMS, RMvD, WJHJM, ALV, PDG, MDL, GMvD, NDB, LPSS all made substantial contributions to the conception and design of the study. RMS undertook pilot scoring and provided refinement of outcome measure adjudication methods. JvdB and RMS drafted the manuscript under supervision of LPS. All authors provided critical review and final approval of the present manuscript.

Funding: the RCT will in part be funded by Karl Storz GmbH (Tuttlingen, Germany), who will also provide the fluorescence imaging equipment. Half of the needed ICG will be provided by Diagnostic Green (Aschheim, Germany). 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; peer reviewed for ethical approval prior to submission.

List of participating sites: Approval is obtained for the following sites: Maastricht University Medical Center+ (MUMC+, Maastricht, The Netherlands), Leiden University Medical Center (LUMC, Leiden, The Netherlands); University Medical Center Groningen (UMCG, Groningen, The Netherlands); Amphia Hospital (Breda, The Netherlands); Catharina Hospital (Eindhoven, The Netherlands). Several centers outside the Netherlands will be approached after the trial has fully started in the national centers. Maastricht University Center will be the coordinating center. The investigators from Maastricht University Medical Center will manage, analyze and interpret the data primarily.

Protocol version: This manuscript is bases on protocol version 4, submitted to the Medical Ethical Committee Maastricht University Medical Center/ University of Maastricht on November 2nd 2016

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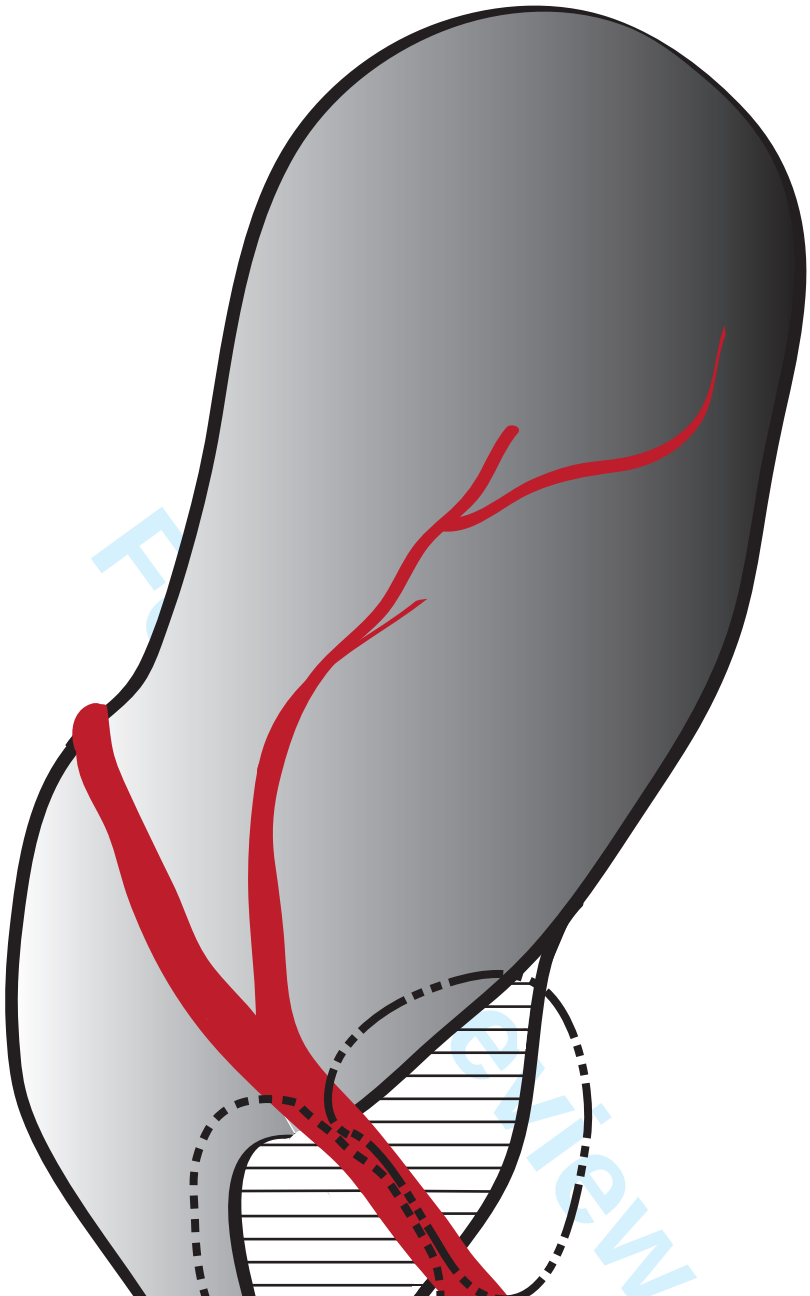


Window of CVS between cystic artery, cystic duct and gallbladder

Window of CVS between cystic artery, gallbladder and liver

Gallbladder bed where detatched from liver

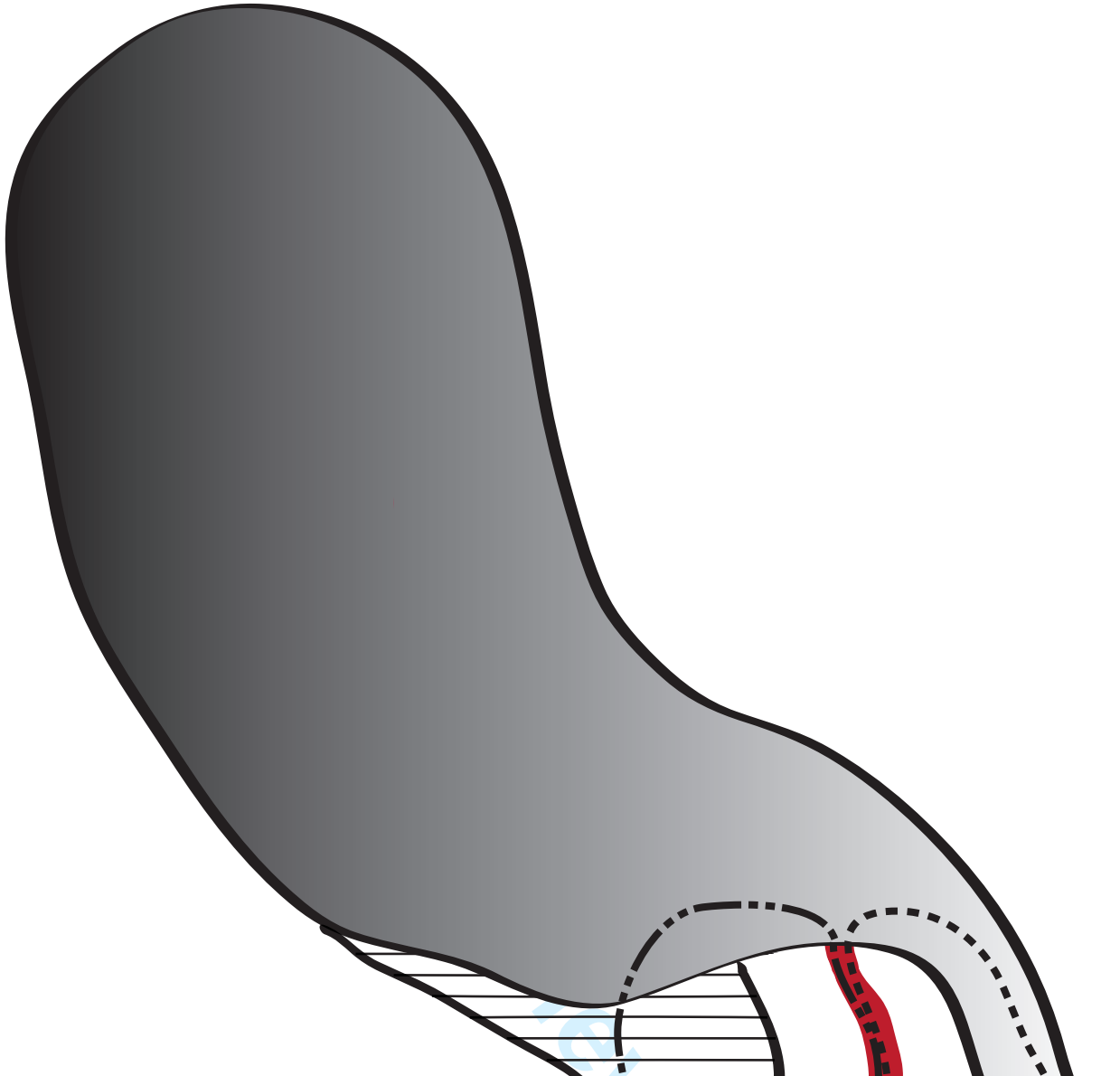


Figure 2a – Flow chart of study procedures: NIRF laparoscopic cholecystectomy (NIRF-LC) group

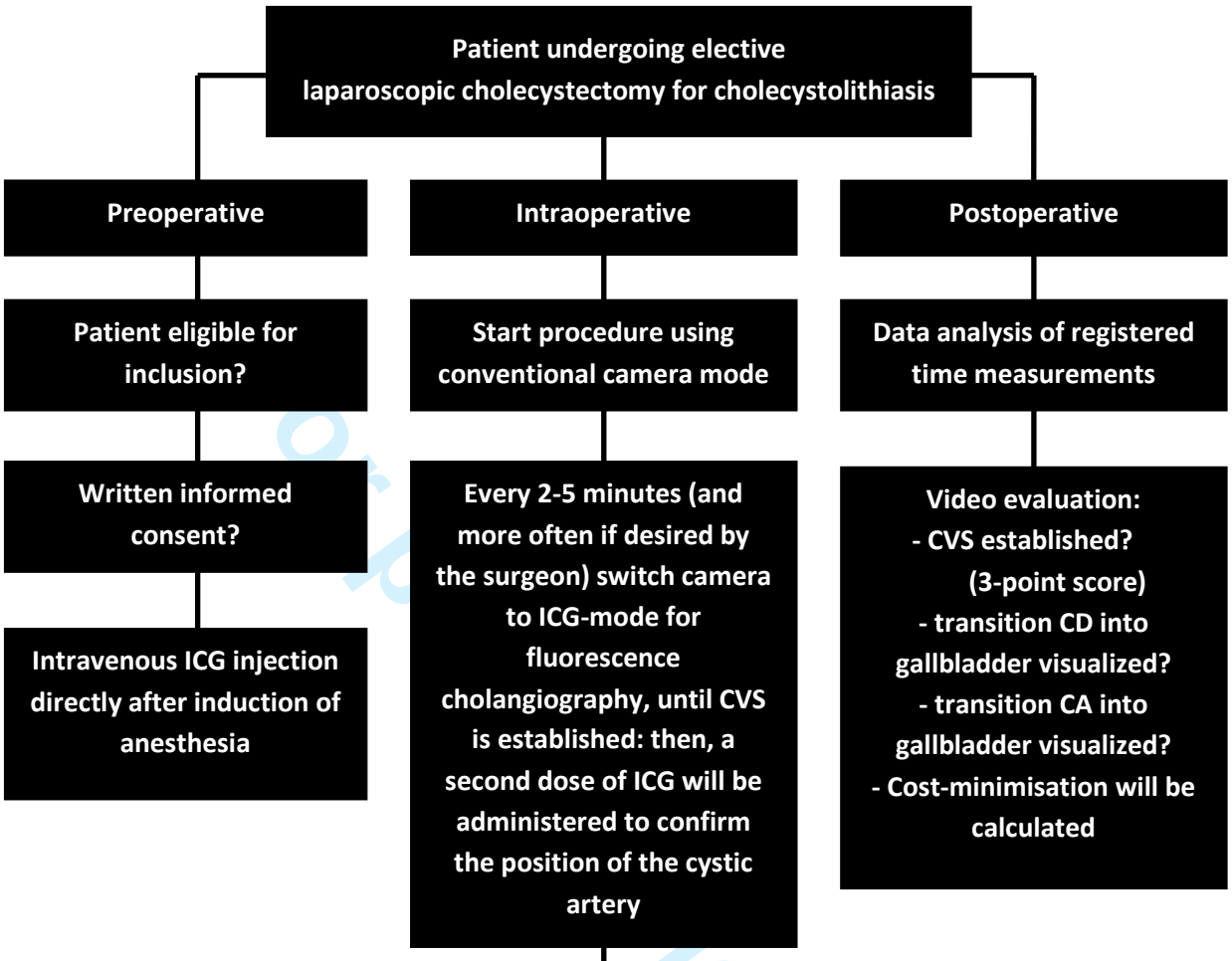


Figure 2b – Flow chart of study procedures: conventional laparoscopic cholecystectomy (CLC) group

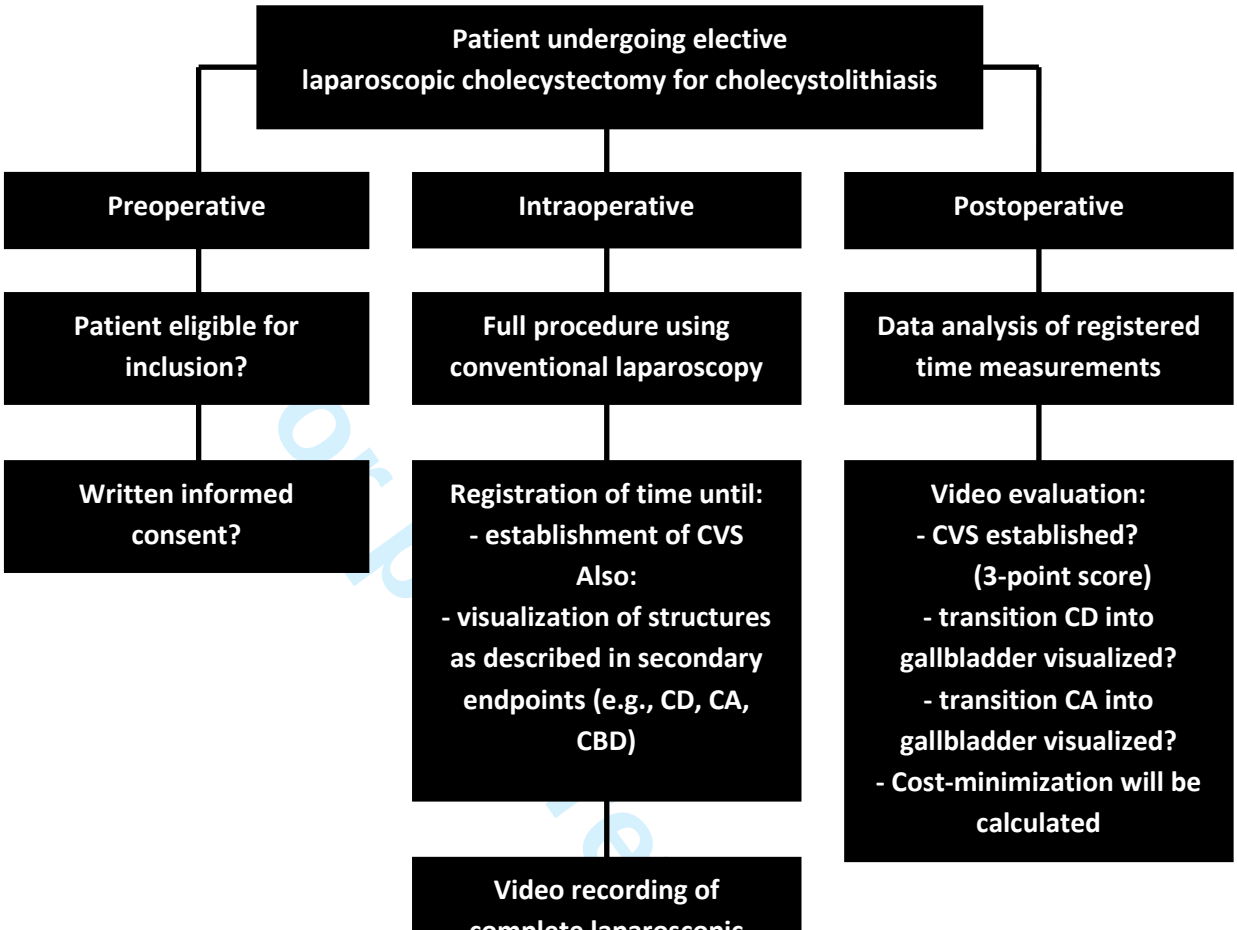
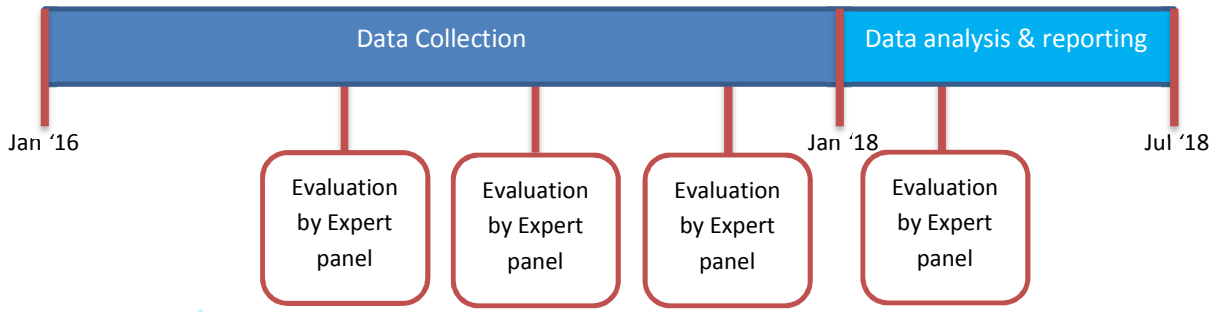


Figure 3: Study timeline



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on 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 registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	14
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	13
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

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 and 5_____
	6b	Explanation for choice of comparators	_____5_____
Objectives	7	Specific objectives or hypotheses	_____6_____
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, noninferiority, exploratory)	_____6_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____6_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____7_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_not applicable__
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_not applicable__
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_not applicable__
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____7-9_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____10_____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____6_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____10_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____7_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____7_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____7_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____7_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_not applicable__
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____9_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_not applicable__

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10-11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10-11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
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	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Near-infrared Fluorescence Cholangiography assisted Laparoscopic Cholecystectomy versus Conventional Laparoscopic Cholecystectomy (FALCON trial): study protocol for a multicenter randomized controlled trial.

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Secondary Subject Heading:	Gastroenterology and hepatology, Research methods
Keywords:	Near-Infrared Fluorescence Imaging (NIRF), Indocyanine Green (ICG), Laparoscopic Cholecystectomy (LC), Critical View of Safety (CVS), Bile duct Injury

Near-infrared Fluorescence Cholangiography assisted Laparoscopic Cholecystectomy versus Conventional Laparoscopic Cholecystectomy (FALCON trial): study protocol for a multicenter randomized controlled trial.

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Trial registration

ClinicalTrials.gov, number NL47718.068.14

Trial number ID NCT02558556

ABSTRACT

Introduction:

Misidentification of the extra-hepatic bile duct anatomy during laparoscopic cholecystectomy 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 intravenous injection of indocyanine green (ICG). Promising results were reported for successful intraoperative identification of the extra-hepatic 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 multicenter randomized clinical study was designed to assess the potential added value of the NIRF-imaging technique during laparoscopic cholecystectomy.

Methods and Analysis:

A multi-center, randomized controlled clinical trial will be carried out to assess the use of NIRF imaging in laparoscopic cholecystectomy. In total 308 patients scheduled for an elective laparoscopic cholecystectomy will be included. These patients will be randomized into a NIRF-imaging laparoscopic cholecystectomy (NIRF-LC) group and conventional laparoscopic cholecystectomy (CLC) group. The primary endpoint is time to 'Critical View of Safety' (CVS). Secondary endpoints 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-minimization".

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.

Article summary:

Strengths and limitations of this study:

- Strength: this study is a randomized controlled multicenter trial.
- Strength: the study addresses a clinically important topic: safety of laparoscopic cholecystectomy

- Strength: operative endpoints will be assessed in a dual manner: preoperatively, but also by an expert panel postoperatively based on video analysis.
- Limitation: a more preferable primary endpoint would have been 'bile duct injury'; however, this is not achievable since very large sample sizes would be required for sufficient power.

Keywords

Near-Infrared Fluorescence Imaging (NIRF), Indocyanine Green (ICG), Laparoscopic Cholecystectomy (LC), Critical View of Safety (CVS)

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, multi-organ failure and eventually death. Therefore, early recognition and treatment is important (7, 11). Misidentification of the extra-hepatic bile duct anatomy during laparoscopic cholecystectomy 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 Critical View of Safety 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, cystic duct and gallbladder, another between the cystic artery, gallbladder and liver (see figure 1a and 1b). The CVS technique is especially aimed at mobilizing the gallbladder neck from the liver, in order to obtain a circumferential identification of the transition of the cystic duct (CD) into the gallbladder. The CVS technique is the gold standard nowadays 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, only in 10% of the laparoscopic cholecystectomies CVS is actually established (22). 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 to identify the relevant anatomical structures easier, such as intraoperative cholangiography (IOC) and near-infrared fluorescence (NIRF) imaging. 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 laparoscopic cholecystectomy, as the procedure takes time, radiation exposure is involved and additional equipment and manpower for the procedure are required. 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 intraoperative cholangiography is still lacking (24).

Near-infrared fluorescence (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 is required, making it an easy, real-time and flexible technique to use technique during surgery. By real-time identification of the vital structures being the cystic duct and common bile duct within the already adapted CVS technique, it may improve the outcome of laparoscopic cholecystectomy (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 identification of the common bile duct and the cystic duct, compared to conventional laparoscopic imaging. Furthermore, a clinical study (n=30) showed that the NIRF imaging technique provided significantly earlier identification of the extra-hepatic bile ducts during the CVS dissection phase: up to 10 minutes earlier identification of the cystic duct and common bile duct could be obtained (35). Real-time imaging of the hepatic and cystic arteries was also achieved when given 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 multicenter randomized clinical study was designed to assess the added value of the NIRF imaging technique during laparoscopic cholecystectomy. 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 Critical View of Safety can be obtained using the NIRF imaging technique during laparoscopic cholecystectomy.

METHODS AND ANALYSIS

Primary aim: The main objective of the study is to evaluate whether earlier establishment of the Critical View of Safety can be obtained using the NIRF imaging technique during elective laparoscopic cholecystectomy, by applying NIRF imaging as an adjunct to conventional laparoscopic imaging versus conventional laparoscopic imaging alone.

Hypothesis: It is hypothesized that standard application of NIRF imaging during laparoscopic cholecystectomy will result in establishment of Critical View of Safety at least 5 minutes earlier and with more certainty regarding visualization of biliary anatomy when compared to conventional laparoscopic imaging alone.

Study design: A multicenter randomized controlled clinical trial, with two randomization arms: a NIRF-LC (laparoscopic cholecystectomy) group: this group of patients will undergo NIRF cholangiography assisted laparoscopic cholecystectomy; a CLC (conventional laparoscopic cholecystectomy) control group: this group will undergo conventional laparoscopic cholecystectomy.

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 centers has started, international centers will be included.

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

Sample size calculation: The number of 308 participants is based on pilot data (35, 38) in which identification of the cystic duct and common bile duct was established respectively 11 and 10 minutes earlier using fluorescence laparoscopic imaging compared to conventional laparoscopic imaging. A sample size of 131 for each randomization arm has been calculated to detect a reduction in 'time to establishment of CVS' of at least 5 minutes with a power of 80% and an α of 0.05 (95%-confidence). Assuming a withdrawal rate of 15% (due to usual reasons for drop-out in combination with technical difficulties concerning the video recordings) during the trial, a total of 308 (n = 2 x 131 + 15%) will be required

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

Inclusion criteria: Male and female patients, aged 18 years and above, scheduled for elective laparoscopic cholecystectomy, 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, Physical Status Classification of ASA I / ASA II.

Exclusion criteria: 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.

Subjects 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 subject 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 endpoints. There are no other specific criteria for withdrawal. In case of withdrawal, individual subjects will be replaced to achieve the calculated sample size. All inclusions will be analyzed on an intention-to-treat basis.

Randomization: All included patients will be randomized centrally using block randomization with sealed envelopes and stratification per participating center. 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 (CLC). 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 cystic artery a NIRF contrast agent will administered. Directly after induction of anesthesia 2,5 mg of Indocyanine Green (ICG) (2.5mg/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 endpoint is used as a surrogate for bile duct identification without surgical exploration. CVS is established if the following three criteria are met:

1. Mobilization of the gallbladder infundibulum for 1/3rd of the length of the gallbladder from the liver bed
2. Circumferential exposure of the cystic duct and confirmation of its transition in the gallbladder
3. Circumferential exposure of the cystic artery and confirmation of its transition in the gallbladder

Secondary outcome measures are listed in table 1:

Table1: Secondary outcome measures

Outcome measure	**Definition**
Time until identification of the cystic duct (CD)	Time in minutes
Time until identification of common bile duct	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 cystic artery (CA) into the gallbladder	Time in minutes
Total Surgical time	Time in minutes from skin incision to the end of skin closure
Visualization of CVS and visualization of the transition of the cystic duct and cystic artery into the gallbladder	Time in minutes
Intraoperative bile leakage from the gallbladder or cystic duct	Visualized 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 cystic duct 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 Minimization	Difference in costs (in Euros) between conventional LC and NIRF LC

Data collection: Intra-operatively a Case Report Form will be filled in. A structure is scored as 'identified' if its localization 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 analyze the data using video recordings: time until identification of the cystic duct and of its transition into the gallbladder; time until identification of the cystic artery and its transition into the gallbladder during dissection of CVS; 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 endpoints. Mean values of these five assessments will be used for each of the endpoints. All clinical data are prospectively registered in a database.

OsiriX 5.5.1. Imaging Software (Prixmeo, Geneva, Switzerland) will be used for objective assessment of the degree of fluorescence illumination in the extra-hepatic bile ducts. The fluorescence images will be analyzed by determining target-to-background ratio (TBR). TBR is defined as the mean fluorescence intensity (FI) of two point regions of interest (ROIs) in the target (i.e. CBD, CD or CA) minus the mean fluorescence intensity of two background (BG) ROIs in the liver hilum, divided by the

mean fluorescence intensity of the two background ROIs in the liver hilum; in formula: TBR = (FI of target – FI of BG) / FI of BG.

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

In figure 2a and 2b, a flowchart of the study procedure for both the NIRF-LC group and the C group is presented.

Data validation and management: Patient data will be anonymously registered and analyzed 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 endpoints; 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 randomized in the NIRF-LC group. After surgery a 90day follow-up period follows after which possible complications will be evaluated.

Statistical analysis: For statistical analysis, the most recent version of SPSS (IBM, Armonk, NY, USA) will be used. Baseline characteristics such as patient clinical history (including previous surgery), age, Body Mass Index, 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 Chi-Square 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 standard deviation. 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 NIRF imaging technique compared to CLC.

All numerical secondary outcomes such as time until visualization of cystic duct and cystic artery will be analyzed 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 cystic duct or cystic artery 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 analyzed 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 Clinical Trial Center Maastricht (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 send to the Medical Ethics committee of Maastricht University Medical Center / Maastricht University. After approval the changes will be communicated in the registration on clinicaltrials.gov and to the- relevant parties.

1. 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 multicenter randomized clinical study can provide such data.

2. 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 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 less than 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 edema, 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, slowly administer antihistamines intravenously. In case of an anaphylactic shock, the patient will be placed in recumbent position with legs raised, volume will be rapidly substituted with e.g. isotonic electrolyte solution (pressure infusion), plasma expanders. And 0.1-0.5 mg adrenaline will be administered immediately diluted to 10 ml with 0.9% saline intravenously. If necessary, this will be repeated after 10 minutes

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

3. Do the individuals give informed consent?

To each patient that is a potential candidate for inclusion thorough patient information will be given. From each subject that 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, both 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.

Dissemination: The findings of this study will be disseminated widely through peer-reviewed publications and conference presentations. Participants have an option in their informed consent form to be informed of the study results after the study. These patients will receive a short communication written on patient-level. There are no publication restrictions for this trial.

Contributors: JvbB, RMS, RMvD, WJHJM, ALV, PDG, MDL, GMvD, NDB, LPSS all made substantial contributions to the conception and design of the study. RMS undertook pilot scoring and provided refinement of outcome measure adjudication methods. JvdB and RMS drafted the manuscript under supervision of LPS. All authors provided critical review and final approval of the present manuscript.

Funding: the RCT will in part be funded by Karl Storz GmbH (Tuttlingen, Germany), who will also provide the fluorescence imaging equipment. Half of the needed ICG will be provided by Diagnostic Green (Aschheim, Germany). 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; peer reviewed for ethical approval prior to submission.

List of participating sites: Approval is obtained for the following sites: Maastricht University Medical Center+ (MUMC+, Maastricht, The Netherlands), Leiden University Medical Center (LUMC, Leiden, The Netherlands); University Medical Center Groningen (UMCG, Groningen, The Netherlands); Amphia Hospital (Breda, The Netherlands); Catharina Hospital (Eindhoven, The Netherlands). Several

centers outside the Netherlands will be approached after the trial has fully started in the national centers. Maastricht University Center will be the coordinating center. The investigators from Maastricht University Medical Center will manage, analyze and interpret the data primarily.

Protocol version: This manuscript is based on protocol version 5.2, submitted to the Medical Ethical Committee Maastricht University Medical Center/ University of Maastricht on April 7th 2016

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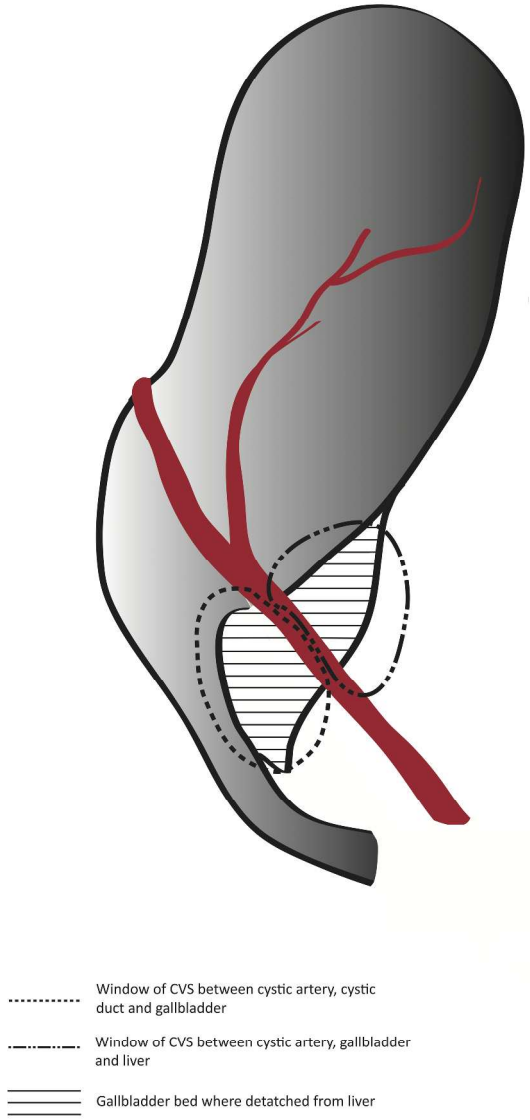
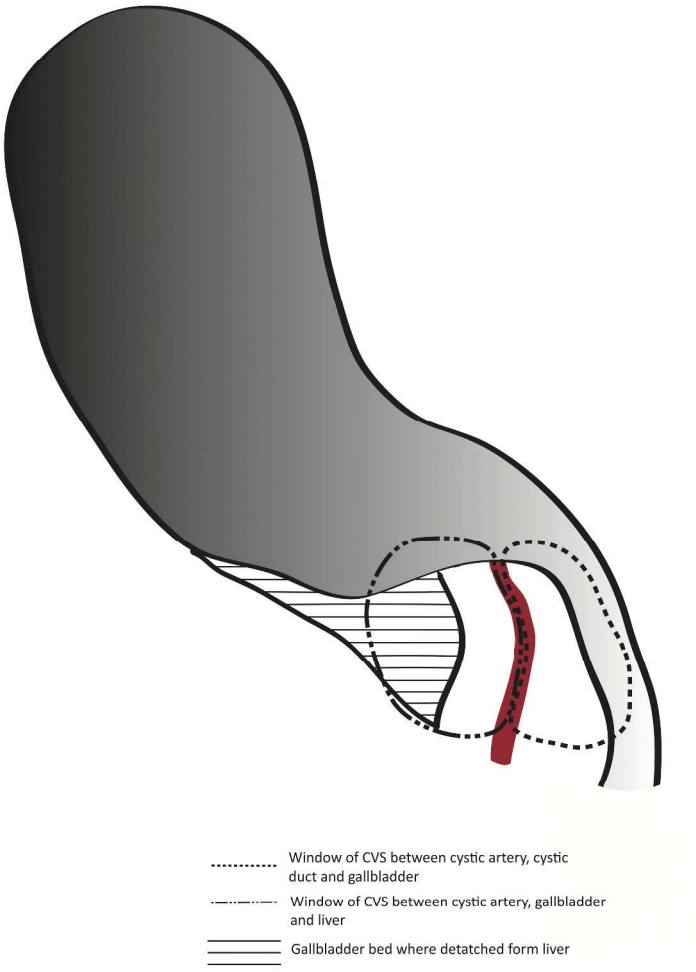
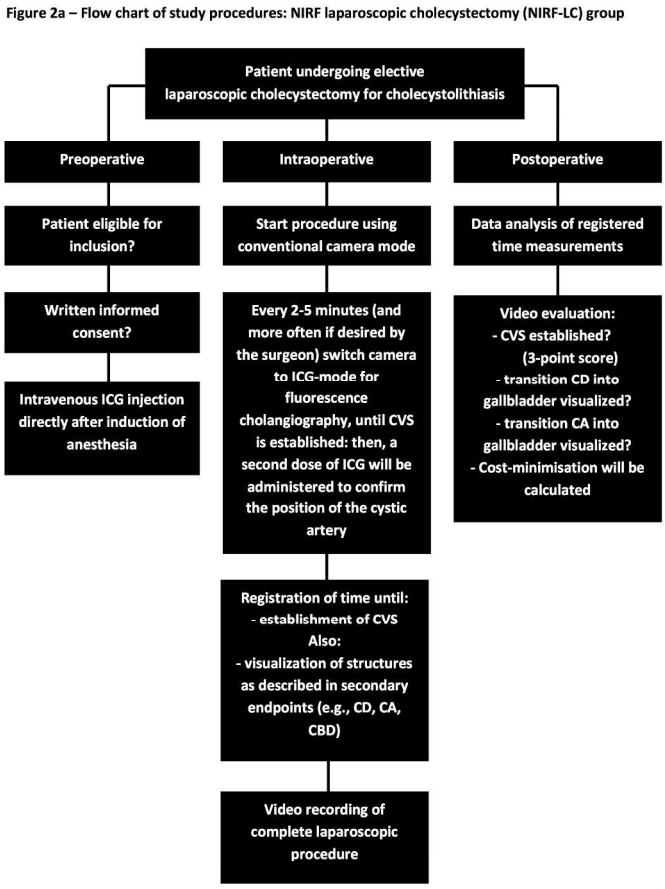


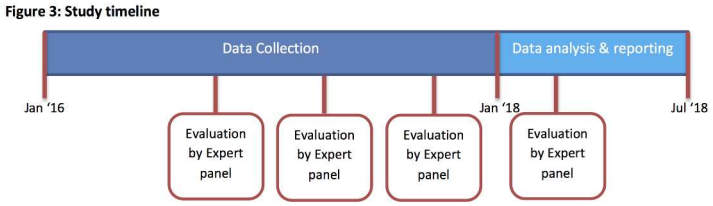
CVS Anterior View: two windows are created. One window between the cystic artery, cystic duct and gallbladder, the other between the cystic artery, gallbladder and liver.
Figure 1a
296x419mm (300 x 300 DPI)



CVS Posterior View: two windows are created. One window between the cystic artery, cystic duct and gallbladder, the other between the cystic artery, gallbladder and liver.
Figure 1b
296x419mm (300 x 300 DPI)



Flow chart of study procedures
Figure 2a and 2b
209x297mm (300 x 300 DPI)



Study timeline
Figure 3
209x297mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on 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 registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	14
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	13
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6 and 13

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 and 5_____
	6b	Explanation for choice of comparators	_____5_____
Objectives	7	Specific objectives or hypotheses	_____6_____
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, noninferiority, exploratory)	_____6_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____6_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____7_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_not applicable__
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_not applicable__
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_not applicable__
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____7-9_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____10_____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6~~10~~
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	not applicable

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10-11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10-11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	132
	31b	Authorship eligibility guidelines and any intended use of professional writers	132
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
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	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.