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Dose and administration time of indocyanine green in near-infrared fluorescence cholangiography during laparoscopic cholecystectomy (DOTIG): study protocol for a randomised clinical trial

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ABSTRACT

Background One of the most severe complications in laparoscopic cholecystectomy (LC) is intraoperative bile duct injury (BDI). Despite its low incidence, the medical implications for the patient can be serious. Besides, BDI can also generate significant legal issues in healthcare. Different techniques have been described to reduce the incidence of this complication, and near-infrared fluorescence cholangiography with indocyanine green (NIRFC-ICG) is one of the latest additions. In spite of the great interest aroused by this procedure, there are currently great disparities in the usage or administration protocols of ICG.

Methods and analysis This is a randomised, multicentre, per-protocol analysis, open clinical trial with four arms. The estimated duration of the trial is 12 months. The aim of the study is to analyse whether there are differences between the dose and administration ICG intervals to obtain good-quality NIRFC during LC. The primary outcome is the degree of identification of critical biliary structures during LC. In addition, different factors will be analysed that may have an influence on the results of this technique.

Ethics and dissemination The trial will be conducted according to the recommendations for Clinical Trials in the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and the recommendations of the Spanish Agency of Medicines and Medical Devices (AEMPs) for clinical trials. This trial was approved by the local institutional Ethics Committee and the AEMPs. The results of the study will be presented to the scientific community through publications, conferences or other means.

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Trial registration number NCT05419947.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Randomised clinical trial that attempts to find differences in the visualisation rates of extrahepatic biliary structures with different doses and administration intervals of indocyanine green (ICG).
⇒ Future possibilities to create a protocol and generalise adequate doses and administration intervals for ICG.
⇒ However, only four arms are assessed (the most common ones found in the literature), and there are multiple possible combinations.
⇒ Subjective visual assessment of the targets.

INTRODUCTION

Symptomatic cholelithiasis has a major worldwide impact, with prevalence rates of up to 20%. Regardless of the related-symptoms or complications, the gold standard treatment is the laparoscopic cholecystectomy (LC).[1 2] One of the most severe complications is bile duct injury (BDI). Although its incidence is <1%, BDI is associated with increased morbidity and mortality, poorer quality of life, increased health costs and medicolegal consequences.[3] One of the main factors in BDI is the misidentification of biliary anatomy,[4] related to anatomic variability and inflammatory changes after complicated cholelithiasis.

One of the techniques that have been developed to avoid BDI is near-infrared fluorescence cholangiography with indocyanine green (NIRFC-ICG). Although this technique has been widely assessed over the last years, currently there are still significant differences in the ICG administration protocols.

The aim of the study is to analyse the differences between the doses and administration intervals of ICG to achieve an optimal visualisation of the extrahepatic biliary anatomy during LC.

METHODS AND ANALYSIS

Objectives

Primary endpoint

Analysing whether there are differences between different doses (fixed or weight-adjusted doses) and ICG administration intervals for an optimal visualisation of biliary anatomy during NIRFC-LC.

Secondary endpoints

- Analysing the influence of the body mass index (BMI) on the results of NIRFC-LC.
- Analysing the influence of the previous biliary disease (biliary colic, choledocholithiasis, cholecystitis, pancreatitis, cholangitis) and previous liver disease (fatty liver, hepatitis, cirrhosis), on the results of NIRFC-LC.
- Analysing the influence of the surgery (elective/early/delayed) on the results of NIRFC-LC.
- Analysing the influence of previous biliary interventions (endoscopic retrograde cholangiopancreatography (ERCP), percutaneous cholecystostomy, endoscopic ultrasound-guided gallbladder drainage) on the results of NIRFC-LC.
- Analysing the influence of the different laparoscopic imaging systems on the results of NIRFC-LC.
- Analysing the rate of intraoperative and postoperative complications related to NIRFC-LC.
- Analysing the impact of NIRFC-LC on general surgeons and their subjective assessment of the procedure.

Design

Prospective, randomised, phase IV, open, multicentre and parallel study with four arms (two doses and two administration intervals). The distribution of the patients is 1:1:1:1. The framework of the study has been designed to observe differences between doses and the time of ICG administration in NIRFC-LC. We adhere to the Standard Protocol Items for Randomized Trials (SPIRIT).[5] The SPIRIT 2013 Checklist is provided in online supplemental file 1.

Study scope

The institutions which participated in the study were the Hospital Universitario de Salamanca and the Hospital Universitario Germans Trias i Pujol. They are both academic medical hospitals in Spain.

Study population

Inclusion criteria

- Age>18 years.
- Self-sufficiency.
- Scheduled LC indication:
  - Surgery for gallstone disease.
  - Surgery for gallbladder polyps.
  - Surgery for gallbladder adenomyomatosis.
- Indication of early LC (<72 hours for admission with acute cholecystitis or biliary colic).
- Delayed urgency LC.
- Understanding the information.
- Signature of the informed consent (online supplemental file 2).

Exclusion criteria

- Age <18 years.
- Disability.
- Pregnancy or lactation.
- Chronic kidney disease (stage>IIIb).
- Previous adverse reactions to ICG.
- Previous adverse reactions to ICG excipients.
- Previous adverse reactions to iodinated contrast agents.
- Functional thyroid disorders.
- Emergency gallbladder surgery.
- Initial laparotomy surgery.
- Previous suspicion of gallbladder cancer.
- Inability to understand the information about the study.
- Refusal to participate in the study.

Interventions

All the patients included in the study will undergo LC with intraoperative NIRFC through intravenous administration of ICG (Verdye (Diagnostic Green GMBH, Achheim-Dornach, Germany)). The administration protocols of this drug will be divided according to the dose and time interval until surgery, as detailed below (figure 1):

- **Dose**: two groups—2.5 mg fixed dose or weight-adjusted dose (0.05 mg/kg).
- **Administration time**: two groups—on admission (>3 hours before surgery) and during the anaesthesia induction (15–30 min before surgery).

Surgery will be conducted based on the criteria for safe LC. The surgeons who will perform this technique have wide experience in the treatment of symptomatic gallstone disease and hepatobiliary disorders. Different imaging systems will be used according to each hospital: 1688 Advanced Imaging Modalities (AIM) 4K Platform (Stryker), IMAGE1 S 4U-LINK/RUBINA, OPAL1 NIR/ICG (Karl Storz-Endoskope) and VISERA ELITE II OTV-S300 (Olympus).

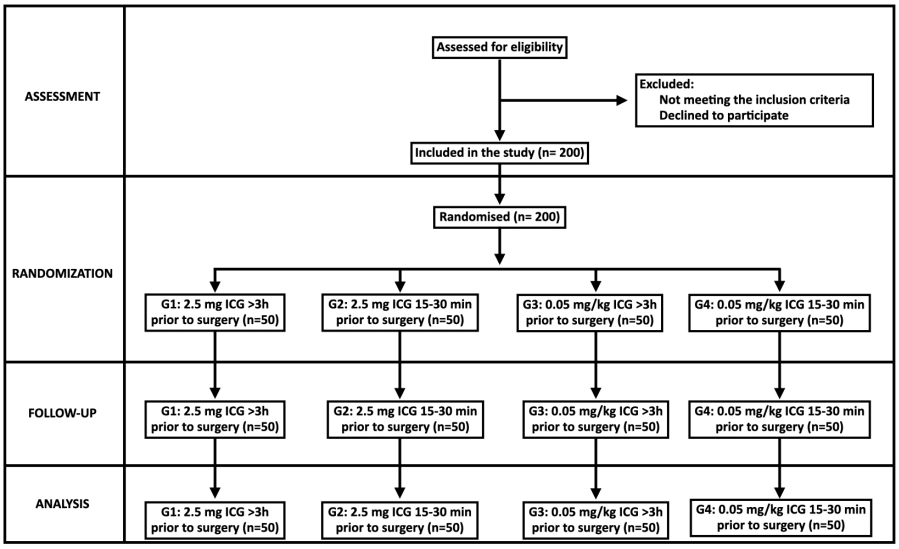
Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

In order to assess the differences between the four treatment groups (primary endpoint), the following target variables will be applied:

1. Visualisation of biliary structures prior to the dissection of the hepatocystic triangle (yes/no):
   - Cystic duct (CD)
   - Common bile duct (CBD)
   - CD–CBD junction
   - CD–gallbladder junction
   - Common hepatic duct.



G1: Group 1, G2: Group 2, G3: Group 3, G4: Group 4, ICG: Indocyanine green

Figure 1 Flow chart for participant eligibility, interventions, assessments and follow-up.

- Anatomical variations.

2. Visualisation of biliary structures after the dissection ofthe hepatocystic triangle (yes/no):
   - Cystic duct (CD)
   - Common bile duct (CBD)
   - CD–CBD junction
   - CD–gallbladder junction
   - Common hepatic duct
   - Anatomical variations
3. Quality of visualisation of biliary structures before dissection of the hepatocystic triangle (1=poor, 2=sufficient, 3=fair, 4=good, 5=excellent).
4. Quality of visualisation of biliary structures after dissection of the hepatocystic triangle (1=poor, 2= sufficient, 3=fair, 4=good, 5=excellent).
5. Extent to which fluorescence cholangiography wasperceived as useful for the surgery (0=not helpful, 1=moderately helpful, 2=very helpful).
6. Extent to which liver fluorescence background (livertoducts contrast) was perceived as a disturbance(0=absence of disturbance 1=lightly disturbed, 2=disturbed visualisation, but CD–CBD junction was clearly visible before dissection, 3=disturbed visualisationand CD–CBD junction was only visible after dissection, 4=heavily disturbed: it was impossible to correctly visualise biliary structures)

The NIRFC-LC assessment will be performed by the main surgeon during surgery (in the case of a procedure performed by a resident surgeon, the assessment will be carried out by the consultant surgeon of the procedure).

In order to assess the secondary endpoints, the following target variables will be applied:

Preoperative variables

1. Date of birth.
2. Age.
3. Sex (female/male).
4. BMI.
5. Previous liver disease (fatty liver/hepatitis/cirrhosis).
6. American Society of Anesthesiologisth (ASA) physical status classification system.
7. Previous abdominal surgeries (no/bile duct/liver/pancreas/bowel/others).
8. Previous biliary techniques (no/ERCP/percutaneous transhepatic cholangiography).
9. Previous biliary stent (yes/no).
10. History of cholecystitis or cholangitis (yes/no).
11. Previous gallbladder drainage (no/endoscopic ultrasound-guided gallbladder drainage/percutaneous cholecystostomy).
12. Indication for surgery (biliary colic/cholecystitis/choledocholithiasis/cholangitis/pancreatitis lithiasis/gallbladder polyps/gallbladder ademoniomatosis).

Perioperative variables

1. Date and time of admission.
2. Date and time of surgery.
3. Type of surgery (elective/early/ delayed).
4. Grade of cholecystitis in case of early or delayed surgery (according to Tokyo Guidelines 2018).
5. Adverse reactions to ICG (yes /no).
6. Number of trocars (3/4).
7. Laparoscopic imaging system (Olympus/Karl-Storz/Stryker).
8. Laparoscope (30°/0°).
9. Conversion to open surgery (yes/no).
10. Surgical complications (yes/ no).
11. Type of surgical complication (liver injury/gallbladder perforation/right hepatic artery injury/cystic artery injury/bowel injury/others).
12. Surgical time (skin incision to wound closure).

Postoperative variables

1. Hospital stay.

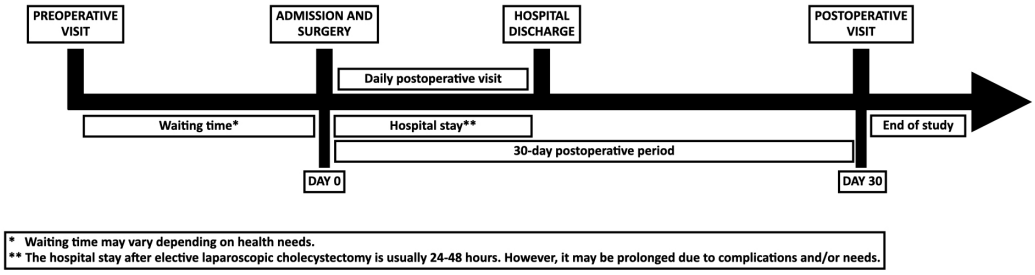


Figure 2 Timeline of the study.

2. Postoperative complications (yes/no).
3. Classification of postoperative complications (Clavien-Dindo classification).
4. BDI (yes/no).
5. Classification of BDI (according to Strasberg classification).
6. Timing of the diagnosis of BDI (during surgery/postoperative period).
7. Treatment of BDI (surgical /radiological/ endoscopic).
8. Hospital mortality (yes /no).
9. Mortality at 30 days (yes/ no).
10. Late adverse reactions to ICG (yes/ no).

Timeline

- Preoperative visit: the aim of the study and the protocol are explained to the patient, and informed consent documents are given to the patient.
- In-hospital preoperative visit: the researchers verify that the patient has understood the information and that informed consent forms have been properly signed.
- Daily postoperative visits: these visits will be conducted by the surgery team.
- Follow-up postoperative visit: it will be conducted 30 days after surgery figure 2.

The expected duration of the subject's participation will be 31 days. This includes the preoperative, intraoperative and the 30-day postoperative periods. The end of the clinical trial will take place 30 days after discharge of the last recruited patients in order to analyse morbidity and mortality after 30 days (figure 2).

Sample size

In order to estimate the sample size, an annual average of 300 LC was estimated. Assuming a minimum recruitment rate of 50%, a duration of 12 months and the potential loss of patients, we estimated a sample size of 200 patients. Since the primary endpoint is to analyse whether there are differences between doses and administration intervals in the four arms in which categorical variables are measured, the effect of the chosen sample size (n=200) on the statistical contrasts in this type of variables is w=0.25, with a power of ®=0.95 and a cut-off point of significance for the rejection of the null hypothesis of ≤0.05.

Recruitment

The annual rate of LC in the two hospitals in the study is over 300 surgeries per year. In order to recruit 200 in both centres, a review waiting list will be conducted. Patients who meet the inclusion criteria will be given the necessary information and, after signing the informed consent form, will be included in the trial.

Randomisation

The subject's randomisation will be conducted using a computer-generated random number. The electronic case report form (eCRF) will be used to implement a block randomisation method with a sequence of 1:1:1:1. Since this trial has no control group, blinding is not considered. The principal investigator (PI) will have access to the eCRF and will generate the randomisation sequence.

Statistical analysis

The Kolmogorov-Smirnov and Shapiro-Wilk test will be used to study the distribution of quantitative variables. These variables are presented as mean (SD) or median (median absolute deviation) according to their distribution. The relationship between these variables will be measured with Pearson's or Spearman's rank correlation coefficient. The distribution of categorical variables will be studied with frequencies and percentages. χ^2 test, Fisher's exact test, McNemar's test or Cochran's Q test will be used to assess the relationships among categorical variables. In order to analyse the influence that some categorical variables may have on the quantitative variables, ANOVA tests may be performed. Finally, all the statistical information obtained on the relevance of each variable in the study may be used to apply classification tools to the subjects of the study (decision trees, logistic regression, ROC curves).

The procedure used to measure missing data will be the pairwise deletion method. The statistical significance will be established at p values <0.05. All the analyses will be performed with the free software R (V.4.1.2+, R Core Team, Vienna, https://www.R-project.org/) and the interface RStudio (V.1.2.1103+).

The study will not include scheduled intermediate analyses, because a partial analysis of the results will not be conducted. When the data are collected, verified and validated a statistical analysis will be performed according to the instructions established in the protocol. If the analysis

reveals the need for further analyses, this will be stated in the final report of results. All the subjects who received treatment and can be assessed will be analysed.

Data management and monitoring

Data collection, management, and analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at Asociación Española de Cirujanos (AEC; www.aecirujanos.es)[6 7].AEC is a non-profit Scientific and Medical Society focused on General and Digestive Surgery and provides this service free of charge, with the sole aim of promoting independent investigator-driven research. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Monitoring

The Data Monitoring Committee (DMC) is appointed by the sponsor, and it includes the clinical trial manager and two clinical trial monitors (one for each centre). The main tasks of the DMC are training all the researchers in the initial visit, checking the veracity of the data, and ensuring protocol compliance with successive visits during the recruiting period. The monitor will supervise the process and contact the centre regularly.

The sponsor will provide instructions and training to the research staff prior to the start of the trial. They will carry out regular monitoring according to the ICH guidelines for GCP. The data will be assessed for protocol compliance and accuracy. The monitors will verify that the trial is conducted, that the data are generated, documented and reported in accordance with the protocol, good clinical practice and any other local applicable regulatory requirements. Direct access to the data will be granted to the PI, monitors, members of the Ethics Committee and the AEMPs and to the necessary authorities, in order to enable monitoring and surveillance of the trial for audit. Auditor's reports will be confidential.

The study interruption criteria are the following:

- Severe adverse events related to drug administration.
- Development of any exclusion criteria within the inclusion period and before surgery.
- Voluntary withdrawal of previously recruited patients.

All the adverse events will be registered in the eCRF. The severity of the event and its relationship with the trial will be assessed according to specific guidelines. Adverse events will be registered after the subject has been randomised. Subjects with adverse events will be monitored by the researcher until they are solved or the patient has been stabilised. The PI must report all severe adverse events within 24 hours.

Annual safety reports will be submitted by the sponsor to the AEMPs, the regional authorities and the Ethics Committee.

Trial Sponsor

Fundación Instituto de Estudios de Ciencias de la Salud de Castilla y León (IESCYL)-Instituto de Investigación Biomédica de Salamanca (IBSAL). Universidad de Salamanca, Salamanca, Spain.

ETHICS AND DISSEMINATION

The trial will be conducted according to the recommendations for Clinical Trials in the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and the recommendations of the AEMPs for clinical trials. This study guarantees compliance with the ICH harmonised tripartite guideline for good clinical practice (GCP). This trial was approved by the local institutional Ethics Committee (IRB: Comité Ético de Investigación con Medicamentos-CEIm- del Área de Salud de Salamanca) and the AEMPs.

The patients will be identified with a code. The researcher will inform the patients that the data obtained in the trial will be stored and analysed digitally, in compliance with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and to Spanish Organic Law 3/2018 of 5 December on Protection of Personal Data.

The PI does not have any interests that may affect the veracity of the data in the clinical trial. Regardless of the results of the study, the sponsor has agreed to present them to the medical community through publications, conferences, or other means.

Dissemination plan

Key message

The clinical trial is seeking participants to analyse the fluorescence cholangiography during LC. The trial is safe, ethical and has the potential to improve the results of LC.

Channels

- Community outreach: informational sessions at local healthcare centres.
- Collaboration with healthcare professionals: work with healthcare professionals such as doctors and nurses to educate them on the trial and encourage them to recommend participation to eligible patients.

Materials

- Presentations to be given at informational sessions.
- Social media posts and online ads to promote the trial and share information.

Implementation

- Schedule informational sessions to promote participation.

- Work with healthcare professionals to educate them on the trial and encourage them to recommend participation to eligible patients.

Evaluation

- Track the number of participants enrolled in the trial.
- Assess the effectiveness of the informational sessions, media advertising and social media outreach (newsletters).
- Make necessary adjustments to the dissemination plan based on the evaluation results.

DISCUSSION

BDI during LC is one of the most severe complications in general surgery. It is associated with high morbidity and mortality rates, need for reinterventions, increased hospital stay and costs, poorer quality of life and legal issues.[3 8–11]

Over the last decades, multiple recommendations have been issued in an attempt to reduce BDI. The best-known one is the Critical View of Safety, published by Strasberg in 1995.[12] This technique is the current standard during safe LC.[13] Other techniques, such as the B-SAFE rule, are still in their implementation stage.[14] One recent approach that combines artificial intelligence and machine learning has been applied to LC to try to improve the safety of the procedure.[15] On the other hand, intraoperative cholangiography (IOC) has been the most frequently used system for the prevention and early detection of BDI, as well as for the diagnosis of choledocholithiasis.[16] However, some of its disadvantages are the use of ionising radiation, its learning curve, the need for prior surgical dissection and other structural problems and needs.[17] In addition, IOC is often performed to rule out a BDI during surgery, rather than to prevent it. In spite of the multiple technical and technological innovations available, there are still cases of BDI during LC.

NIRFC is a recent technique[18] that applies the fluorescent properties and exclusively biliary excretion of ICG to map the extrahepatic biliary tract.[3] ICG has been previously described in cardiology, ophthalmology and hepatology.[19] NIRFC is a fast, real-time visualisation method with a minimal learning curve and no increase in operation times. In addition, it does not require the prior dissection of the hepatocystic triangle and has a lower cost than IOC. However, it is not currently widespread and requires a specific image processing hardware.[17 20]

Recently, NIRFC has shown superiority to LC with white light alone to prevent BDI,[21 22] and a recent meta-analysis estimates that this technique could decrease this complication.[23] There are wide variations in the ICG administration protocols. A correct dose and administration interval are key to achieve an adequate identification of the biliary structures and to reduce the fluorescence emitted by the liver parenchyma, which could be a handicap during the surgery.[24] There are several administration protocols for ICG, either with a fixed dose or with a weight-adjusted dose. The ICG administration intervals also vary widely.[24] Some authors showed lack of liver parenchyma fluorescence when ICG is administered 24 hours before surgery.[25] However, in the context of short-stay surgery, this does not seem to be a viable option. The preliminary results from the IHU-IRCAD-EAES EURO-FIGS reveal several differences in the protocols for preoperative administration of ICG.[26] Therefore, we believe that it is necessary to establish a protocol for the administration of this drug based on the results of randomised clinical trials.

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Contributors JLS is the PI; he designed the study, wrote the protocol and the manuscript. FPA is the PI, he contributed to the design of the study and the protocol. SGM contributed to designed the protocol and write the manuscript. CGS contributed to write the manuscript. RLP is the study manager and he contributed to the review and writing of the protocol. PR-F is the head of Pharmacovigilance and helped write the protocol. JMSS will conduct the statistical analysis of the trial. LMB is the coordinating investigator of the study, helped to design it, write the protocol and he has reviewed the manuscript. All authors approved the final version of the manuscript.

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Competing interests None declared.

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

Patient consent for publication Not applicable.

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SPIRIT Checklist for *Trials*

Complete this checklist by entering the page and line numbers where each of the items listed below can be found in your manuscript.

Your manuscript may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please state "n/a" and provide a short explanation. **Leaving an item blank or stating "n/a" without an explanation will lead to your manuscript being returned before review.**

Upload your completed checklist as an additional file when you submit to *Trials*. You must reference this additional file in the main text of your protocol submission. The completed SPIRIT figure must be included within the main body of the protocol text and can be downloaded here: http://www.spirit-statement.org/schedule-of-enrolment-interventions-and-assessments/

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

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

	Reporting Item		Page and Line Number	Reason if not applicable
Administrative information				
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1, lines 2-4]	
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 3, lines 27-29]	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Page 3, lines 27-29]	
Protocol version	#3	Date and version identifier	Page 3, line 31]	

Funding	#4	Sources and types of financial, material, and other support	Page 14, lines 19-23]	
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 1, lines 5-33]	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 11, lines 21-25]	
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 14, lines 2-10 and lines 19-23]	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 10, lines 29-33]	
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	Page 4, lines 11-21]	

Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 7, lines 4-8]	
Objectives	#7	Specific objectives or hypotheses	Page 5, lines 3-22]	
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	Page 5, lines 23-28]	
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	Page 5, lines 31-33]	
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)	Page 6, lines 1-28]	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 7, lines 1-11]	
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Page 11, lines 8-11]	

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a]	Administration of a single dose]
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 8, lines 20-26]	
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	Page 7, lines 19-29, page 8, lines 1-19]	
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)	Page 8, lines 20-26, Figure 2]	
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	Page 9, lines 1-8]	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 9, lines 9-13]	

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	Page 9, lines 14-19]	
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	Page 9, lines 14-19]	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 9, lines 14-19]	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a]	It is not necessary. No control group]
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a]	It is not necessary. No control group]
Methods: Data collection, management, and analysis				

Data collection plan	#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	Page 10, lines 13-25]	
Data collection plan: retention	#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	Page 10, lines 13-35, page 11, lines 1-6]	
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	Page 10, lines 13-25]	
Statistics: outcomes	#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	Page 9, lines 21-31, page 10, lines 1-11]	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Pages 10, lines 7-8]	

Statistics: analysis population and missing data	#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)	n/a]	Per-protocol study. The procedure used to measure missing data will be the pairwise deletion method]
Methods: Monitoring				
Data monitoring: formal committee	#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	Page 10, lines 27-35, page 11, lines 1-6]	
Data monitoring: interim analysis	#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	Page 11, lines 8-11]	
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	Page 11, lines 13-17]	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Pages 11, lines 13-19]	
Ethics and dissemination				

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 12, lines 1-12]	
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)	Page 12, lines 1-16]	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 8, lines 21-24]	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a]	Included in a single consent]
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	Page 12, lines 8-12]	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 14, line 24]	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 10, lines 34-35, page 11, lines 1-6]	

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a]	Legal provisions covered by the health system]
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 12, lines 30-31]	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Page 12, lines 14-16]	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a]	There is no current plan]
Appendices				
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a]	Not included for current publication in your journal]
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a]	Not included for current publication in your magazine]

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-

INFORMED CONSENT FORM

TITLE: Randomised clinical trial to evaluate the dose and administration time of Indocyanine Green in Near-Infrared Fluorescein Cholangiography during laparoscopic cholecystectomy.

CODE: DOTIG Trial.

EudraCT number: 2022-000904-36.

Version: 2.0.

Sponsor: Biomedical Research Institute of Salamanca (IBSAL).

Principal Investigator:

Jaime López Sánchez MD, PhD
General and Gastrointestinal Surgery Department
University Hospital of Salamanca
Biomedical Research Institute of Salamanca (IBSAL). University of Salamanca

INTRODUCTION

We are writing to inform you about a research study in which you are invited to participate. Our intention is that you receive correct and sufficient information so that you can decide whether or not to participate in this study. To do so, please take the time to read this information sheet carefully and thoroughly and discuss it with whomever you feel appropriate. Ask your doctor or the study staff to explain any words or information that you do not understand clearly, as well as any questions you may have.

If you decide to participate, we will ask you to sign the attached informed consent form. We will provide you with an original copy of this signed and dated document for you to keep and the original document will be kept on file with the rest of the study documentation.

The study has been approved by the Ethics Committee for Research of the University Hospital of Salamanca, in accordance with current legislation, Royal Decree-Law 1090/2015, which regulates clinical trials with medicines, the Ethics Committees for Research with medicines and the Spanish Register of Clinical Studies, Royal Decree-Law 1591/2009 regulating medical devices, Royal Decree-Law 1616/2009 on active implantable medical devices (if applicable), and Circular 7/2004 of the Spanish Agency for Medicines and Medical Devices on clinical research with medical devices.

It has also been designed and will be conducted in accordance with the recommendations set out in the Declaration of Helsinki and the Standards of Good Clinical Practice.

You should be aware that your participation in this study is voluntary and that you may decide NOT to participate. If you decide to participate, you may change your decision and withdraw your consent at any time, without altering your relationship with your doctor or harming your health care.

You should also be aware that you may be withdrawn from the study if the sponsor or investigators deem it appropriate, either for safety or other reasons. In either case, you will receive an adequate explanation of the reason for your withdrawal from the study.

AIM OF THE STUDY

You are invited to participate in the study because you have been diagnosed with symptomatic gallstone disease. The gold standard treatment for your disease is the removal of the gallbladder (cholecystectomy), ideally by minimally invasive approach (laparoscopy).

To avoid some of the complications of laparoscopic cholecystectomy, the use of a tool called near-infrared fluorescein cholangiography has recently been developed. This technique attempts to fluorescently map critical anatomical structures that appear during surgery, using a substance called indocyanine green. This drug is usually administered intravenously and is eliminated through the bile. Thanks to the fluorescent characteristics of indocyanine green, and its biliary elimination, we will be able to obtain real-time and accurate images of the extrahepatic biliary anatomy. This will aid intraoperative anatomical identification and may prevent injury to important structures. However, the administration time and the ideal dose of indocyanine green to obtain an accurate technique is currently not defined. The DOTIG trial (dose and administration time of indocyanine green in near-infrared fluorescein cholangiography during laparoscopic cholecystectomy) will attempt to find the optimal dose and ideal administration time for performing laparoscopic cholecystectomy with fluorescein cholangiography.

STUDY PROCEDURES AND POSSIBLE RISKS AND DISCOMFORTS

All patients that meet the inclusion criteria and have an indication of a laparoscopic cholecystectomy are eligible upon agreement to participate in this study. You will not be able to participate in this study if you have any of the following contraindications: being a minor, pregnancy or breastfeeding at the time of surgery, advanced chronic kidney disease, allergies or adverse reactions to the product, its excipients, to iodinated contrasts or some diseases of the thyroid gland.

The total number of patients planned to be included in the study is 200 subjects. The drug to be administered is called Verdye (Diagnostic Green GMBH, Aschheim-Dornach, Germany) and contains indocyanine green sodium. All patients who agree to enter the study will be administered the drug intravenously at a variable dose and interval prior to surgery. The study will have four treatment groups divided into different doses and times. The doses will be calculated as a fixed dose or a weight-adjusted dose. The administration interval will vary from the time of admission

to the hospital ward to the time of anaesthetic induction. Assignment of the dose and time of administration prior to surgery will be randomised using a computer application.

No biological samples will be collected for research purposes and no procedures or tests will be performed that are not part of routine clinical practice.

All information about this study will be stored in encrypted form, and will be used exclusively for the purposes specified here. In the event that your data is transferred to other research groups, this will always be done in accordance with current legislation, keeping your data coded, in order to carry out studies related to the objectives of this work, and with prior authorisation from the Research Ethics Committee. In the event that the objectives of the research work proposed by other research groups are different from those of the present project, a new consent will be requested.

Indocyanine green (Verdye) is a product authorised by the Spanish Agency of Medicines and Medical Devices (AEMPS) and the European Medicines Agency (EMA). It has been marketed since 2017 for hospital use only and in authorised diagnostic centres. Indocyanine green is approved for diagnostic use in the field of heart, brain, eyeball and liver studies. The drug has been widely used for fluorescein cholangiography since the first study was published in 2009 to the present day. It has been shown to be safe in humans, with a very low rate of adverse events. As a drug approved by the competent health authorities, information on the side effects of indocyanine green (Verdye) is available to everyone. There may be side effects or reactions that you should be aware of. Severe allergic reactions (anaphylaxis) are extremely rare (affecting less than 1 in 10,000 patients). Patients with kidney disease may be more at risk of developing allergic reactions. Only two cases of death have been reported with the use of indocyanine green during cardiology studies (frequency less than 1/330,000 estimated cases). Cases of indocyanine green overdose are unknown at present. No additional risks are foreseen as you will not undergo any procedures outside of standard clinical practice.

You as a study participant will be expected to comply with a number of responsibilities as outlined below:

- Compliance with the scheduled visit during the first postoperative month.
- Report any adverse events or changes in medication, advising that, except in an emergency, do not change the medication you are taking or take other medications or "herbal medicinal products" without first consulting with the study doctor.

Please speak to your study doctor for a complete list of side effects reported with this drug and in any case, if you wish, you will be given the package leaflet for both drugs.

Voluntary participation and withdrawal

You are free to decide whether or not you wish to take part in this study, participation is entirely voluntary. If you decide to participate, you still have the possibility to withdraw at any time, without having to give any explanation, and without any penalty or negative consequences for you. If you change your mind about your data, you have the right to request its destruction or anonymisation, through your doctor/researcher. However, you should be aware that the data obtained in the analyses carried out up to that point may be used for the purposes requested and may be retained in compliance with the relevant legal obligations.

Potential benefits

No direct benefit is expected from your participation in the study. However, the information obtained from this research project may contribute to medical progress and may help other patients in the future. You will not receive any financial benefit from the donation of the samples and the release of the data provided, nor will you have any rights to potential commercial benefits from any discoveries that may be made as a result of the research conducted.

Alternative treatments

If you do not participate in the study, you will receive treatment according to standard clinical practice.

Data protection and confidentiality

All information about your results will be treated in the strictest confidence. Both the centre and the sponsor and research team are responsible for the processing of your data and undertake to comply with the data protection regulations in force, currently Organic Law 3/2018, of 5 December, Protection of Personal Data and Guarantee of Digital Rights and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on Data Protection (RGPD). The data collected for the study will be identified by a code, so that no information that can identify you is included, and only the research team will be able to relate this data to you. Therefore, your identity will not be disclosed to any other person except to the health authorities, when required or in cases of medical emergency. Research Ethics Committees, representatives of the Health Inspection Authority and personnel authorised by the sponsor may only have access to verify personal data, clinical trial procedures and compliance with the standards of good clinical practice (while maintaining the confidentiality of the information).
Your data will be kept under appropriate security conditions and it is guaranteed that subjects cannot be identified through means considered reasonable by people other than those authorised. The research team will analyse your data based on the legitimate interest of achieving

the purposes of the study. The Investigator and the Sponsor are obliged to retain the data collected for the study for at least 25 years after completion of the study. Thereafter, your personal information will only be retained by the facility for your health care and by the research team for other scientific research purposes if you have given your consent to do so and if permitted by applicable law and ethical requirements.

If the results of the study are likely to be published in scientific journals, no personal data of the participants in this research will be provided at any time. We inform you that you have the right to access, rectify or cancel your data, and you may limit the processing of data that are incorrect, request a copy or that the data you have provided for the study be transferred to a third party. To exercise your rights, or in the event that the participant wishes further information about the processing of your personal data, you may contact the principal investigator of the study whose details are specified at the end of this document, the Data Protection Officer of the Regional Health Authority (dpd@saludcastillayleon.es) or our site (protecciondedatos@ibsal.es). We remind you that the data cannot be deleted, even if you stop participating in the trial in order to ensure the validity of the research and to comply with legal obligations. You also have the right to contact the Data Protection Agency if you are not satisfied.

Information on results

At your request, at the end of the study and in accordance with article 27 of the Law 14/2007 on Biomedical Research, you may be provided with information about the results of this research study.

I consent to the future use of the data collected in this research study to carry out other research related to the medical speciality or research area of this study.

YES / NO

I consent to future re-accessing of my medical records to collect data deemed important for further research related to the medical specialty or research area of this study.

YES / NO

Contact details of the research team:

If you have any questions or need further information, please contact:
Name: Jaime López Sánchez
Telephone: +34 923291100

Whatever your decision, both the promoter and the research team would like to thank you for your time and attention.

INFORMED CONSENT

I (Name and Surname) _____

I have read the information sheet I have been given about the study.

I have been able to ask questions about the study.

I have received sufficient information about the study.

I have read the information sheet given to me.

I have spoken to the Researcher _____ I understand that my participation is voluntary.

I understand that I can withdraw from the study:

1. Whenever I want to.
2. Without having to explain myself
3. Without any negative repercussions

I voluntarily agree to participate in the clinical trial and authorise the use of all information obtained. I understand that I will receive a signed copy of this informed consent form.

Participant's signature Date

Name and signature of the researcher Date

Signature of legal representative, family member or person related in fact Date