January 2017

Fluorescent Cholangiography vs White Light for Bile Ducts Identification NCT02702843

Multi-Center Study Protocol

Efficacy of Near Infrared Incisionless Fluorescent Cholangiography (NIFC) during Laparoscopic Cholecystectomy.

CONFIDENTIALITY STATEMENT

This protocol contains proprietary and confidential information.

Acceptance of this document constitutes agreement by the Lead Site Investigator (LSI) that no unpublished information contained herein will be published or disclosed without the prior written approval of the Principal Investigator (PI), except that this document may be disclosed to 1) study personnel under supervision of the LSI who need to know the contents of this document to properly conduct the study and 2) appropriate Institutional Review Boards under the condition that they keep it confidential. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, the PI must be promptly notified of any such disclosure.

Lead Site Investigator Agreement

I, the undersigned, will provide copies of this protocol, any subsequent protocol amendments and access to all information furnished by KARL STORZ to study personnel under my supervision.

I will discuss this material with them to ensure that they are fully informed about the study protocol and the medical device and drug to which it pertains.

I agree to conduct this clinical study according to the protocol described herein, except when mutually agreed upon in writing by the Principal Investigator. I also agree to conduct this study in compliance with all applicable regulations, as well as with the requirements of the appropriate Institutional Review Board and any other institutional requirements.

Lead Site Investigator Signature: _____

Signature Date: _____

Name: _____

Title: _____

Institution: _____

Address: _____

Phone: _____

Email: _____

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1. Summary

Title:	**Efficacy of Near Infrared Incisionless Fluorescent Cholangiography (NIFC) during Laparoscopic Cholecystectomy (LC)**
Primary Objective:	Demonstrate that NIFC performs better than standard white light (WLI) alone in visualizing and identifying extra-hepatobiliary structures (Cystic Duct, Right Hepatic Duct, Common Hepatic Duct, Common Bile Duct, Cystic-CBD junction, Cystic-Gallbladder junction, and any Accessory Ducts) before and after dissection during Laparoscopic Cholecystectomy (LC).
Secondary Objectives:	1. Demonstrate that NIFC is an effective teaching tool to assist students and residents present in the O.R. during the procedure to identify extra-hepatobiliary structures (before/after dissection). 2. Demonstrate that the Time to Clip, which is defined as the time from the moment Calot's Triangle is first visualized to when the clip is applied, is reduced when using NIFC vs WLI alone. 3. Compare the mean number of procedures that required Conversion to Open using NIFC vs WLI alone. 4. Compare the mean Volume of Bleeding using NIFC vs WLI alone. 5. Compare the Incidence rate of Bile Leakage from the liver bed using NIFC vs WLI alone. 6. Compare the Incidence rate of Bile Duct Injury (BDI) using NIFC vs WLI alone. 7. Compare the mean Surgeon Confidence Level using NIFC vs WLI alone.
Indication:	Laparoscopic Cholecystectomy (LC)
Investigational Design:	Two arms multi-center randomized controlled clinical trial with patients randomized by center.
Inclusion/exclusion criteria:	Inclusion Criteria 1. Patients of both genders 2. Minimum age: 18 years old 3. Spoken and written command of the language spoken in the country's center

	4. Ability to understand and follow the study procedures and sign the informed consent Exclusion Criteria 1. Known allergies to iodides 2. Known history of cholangitis, pancreatitis, CBDS's, coagulopathy 3. Known liver disease 4. Women who are pregnant or breastfeeding, or for whom possibility of pregnancy was not ruled out
Number of Subjects:	1,000 patients enrolled across all centers
Target Population:	Male or female subjects undergoing laparoscopic cholecystectomy that fulfil all of the inclusion and none of the exclusion criteria.
Length of Investigation:	Approximately 1 year
Primary Endpoints:	Detection Rate (DR) of each particular extra-hepatobiliary structure during Laparoscopic Cholecystectomy (LC) defined as the total number of patients in which the particular structure is detected before and after dissection in that arm of the Study (WLI or NIFC), divided by the total number of patients in that arm. Extra-hepatobiliary structures to be included in this assessment: Cystic Duct, Right Hepatic Duct, Common Hepatic Duct, Common Bile Duct, Cystic-CBD junction, Cystic-Gallbladder junction, and any Accessory Ducts.
Secondary Endpoints:	1. The DR for students/residents only (apart from experienced surgeons), both before and after dissection. 2. Time to Clip 3. Incidence of Conversion to Open Surgery 4. Volume of Bleeding 5. Incidence of Bile Leakage from the liver bed 6. Incidence of Bile Duct Injury (BDI) 7. Surgeon Confidence Level
Test Device/ Procedure:	Image1 SPIES (Storz Professional Image Enhancement System) Endoscopic ICG Imaging System
Comparator Device/ Procedure:	Standard Image1 SPIES Endoscopic System using white light imaging (WLI) only
Statistical Analysis:	The DR (before and after dissection) between arms will be compared using the chi-square test while the number of

	structures detected will be analyzed using non-parametric tests. Regression models (logistic or generalized mixed models) will be fitted to evaluate if the effect of NIFC on the primary outcomes is modified by the patient's or surgeon's characteristics or the site.

2. Introduction

a. Background

Around 750,000 laparoscopic cholecystectomies are performed in the U.S. every year. This minimally invasive approach has demonstrated to have several advantages like shorter hospital stay, less operative pain and prompt recovery when compared to the open approach (1,2,3,4,5).

Since its first description, the main concern on laparoscopic cholecystectomy has been bile duct injuries, with an estimated incidence rate of between 0.4 and 1 % (6,7,8,9,10). Most common situations involved in a bile duct injury are lack of visualization and tactile feedback, misidentification of structures and anatomic variations (11,12).

Anatomic anomalies have been identified in 19% of patients (13, 14) and hepatic accessory ducts in 8.4% (15,16,17). Different approaches have been proposed to avoid a bile duct injury. Strassberg described the critical view approach of safety dissecting the Calot´s triangle and identifying the cystic artery and extra-hepatic biliary ducts (18,19,20,21,22). Even though the critical view approach of safety proved to be very useful, it could not diminish the rate of bile duct injury (23). Pablo Mirizzi (1931) developed the intraoperative cholangiography (IOC), an invasive method to map the intrahepatic and extra-hepatic bile ducts (24,25,26,27,28,29,30). Although the goal was to diminish the severity of the injuries, there are still disadvantages of this technique including:

- radiation exposure for patient and OR staff,
- risk of bile duct injury – during insertion of the trans-cystic catheter,
- the need of bulky material, and
- increased misidentification of the cystic duct.

Recently, a novel technique to visualize structures using fluorescent light and intravenous dye has been developed.

Near Infrared Incisionless Fluorescent Cholangiography (NIFC) is a medical imaging technique that uses fluorescence to detect properly labeled structures during surgery.

NIFC is performed using imaging devices with the purpose of providing real-time simultaneous information from color reflectance images (white light) and fluorescence emission (near infrared light). One or more light sources are used

to excite and illuminate the sample. Light is collected using optical filters that match the emission spectrum of the fluorophore. Imaging lenses and digital cameras are used to produce the final image.

Fluorescence excitation is accomplished using various kinds of light sources. Halogen lamps have the advantage of delivering high power for a relatively low cost. Using different band-pass filters, the same source can be used to produce several excitation channels from the UV to the near infrared.

NIFC seems to be a promising method for identification of the extra-hepatic biliary anatomy during laparoscopic cholecystectomy. Real utility of the method should be evaluated in different clinical scenarios through a randomized clinical trial.

b. Significance / Rationale

During laparoscopic cholecystectomies, the visualization of the extra-hepatic bile ducts with fluorescence is called Near Infrared Incisionless Fluorescent Cholangiography (NIFC). Fluorescence equipment and a dye are necessary in order to perform a NIFC, but the technique requires no radiation or incision. A fluorescence dye is administrated intravenously at least 45 minutes before the surgery, which is excreted by the liver and the bile duct (31,32,33).

Different publications have described the utility of this technique in order to visualize the extra-hepatic bile ducts (31,32,33,34,35,36,37). There is no doubt that the method is feasible and accurate (38,39,40). But to establish the method as a standard of care or at least as a recommendation, it is important to determine the real impact of this technique during laparoscopic cholecystectomy in different pathologies and patients.

Ishizawa et al (41) demonstrated that NIFC delineated the cystic duct in all 52 patients, and the cystic duct-common hepatic duct junction was visible before dissection of Calot's triangle in 50 patients.

Shols et al published an initial experience with 15 patients. The group found that the common bile duct and cystic duct could be clearly identified at an early stage of the operation and, more important, significantly earlier than with the conventional camera mode. (42)

Cost effectiveness of the technique was validated by Dip et al (35) with a total of 43 patients (21 males and 22 females). Mean age was 49.53 ± 14.35 years old and mean body mass index was 28.35 ± 8 kg/m^2 (2). Overall mean operative time was 64.95 ± 17.43 min. NIFC was faster than IOC (0.71 ± 0.26 vs. 7.15 ± 3.76 min; $p < 0.0001$). NIFC was successfully performed in 43 of 43 cases (100%) and intraoperative cholangiography (IOC) in 40 of 43 cases (93.02%) while in 3 patients IOC was not possible. NIFC was less expensive than IOC (US$14.10 ± 4.31 vs. US$778.43 ± 0.40; $p < 0.0001$). All surgeons found routine use of NIFC useful. Identification rates of extra-hepatic bile duct using NIFC ranges between 71 and 100 % depending on the study (32,33,34,35).

Osayi et al (36) studied eighty-two patients that underwent elective laparoscopic cholecystectomy and compared the use and utility of near infrared

incisionless fluorescent cholangiography (NIFC) vs intraoperative cholangiography (IOC). Mean age and body mass index (BMI) of the patients were 42.6 ± 13.7 years and 31.5 ± 8.2 kg/m2, respectively. Indocyanine green was administered 73.8 ± 26.4 min prior to incision. NIFC was significantly faster to complete than IOC (1.9 ± 1.7 vs. 11.8 ± 5.3 min, $p < 0.001$). IOC was unobtainable in 20 (24.4 %) patients while NIFC did not visualize biliary structures in four (4.9 %) patients. After complete dissection, the rates of visualization of the cystic duct, common bile duct, and common hepatic duct using NIF were 95.1, 76.8, and 69.5 %, respectively, compared to 72.0, 75.6, and 74.3 % for IOC. In 20 patients where IOC could not be obtained, NIFC successfully identified biliary structures in 80 % of the cases. (39)

Spinoglio et al (40) reported 45 cases between July 2011 and January 2012 with NIFC. The rates of visualization were 93 % for the cystic duct, 88 % for the common hepatic duct, and 91 % for the common bile duct prior to Calot's dissection; after Calot's dissection, the rates were 97 % for all three ducts. Mean hospital stay was 1.1 days and there were no bile duct injuries or any other major complications. (40)

The studies described above are observational and so far no randomized clinical trial has been published evaluating the efficacy of NIFC to improve the identification of the extra-hepatic biliary structures. Additionally it would be relevant to investigate the ability of the NIFC to reduce intraoperative bleeding, duration of laparoscopic cholecystectomy. Further, it is central to assess whether NIFC can improve the outcomes in some subpopulation of patients for whom the evaluation and dissection of the Calot's triangle is difficult, e.g. obese patients or patients undergoing inflammatory processes. Finally, the potential use of NIFC as a training tool in laparoscopic surgery is still to be studied.

c. Strengths and Limitations

The strength of the study is the ability to investigate whether the extra-hepatic biliary tract is more visible using NIFC when compared with white light (WLI) alone. It is a multicenter study with diverse patient populations and surgeons from different countries/continents that will validate this method globally.

Limitations may include impossibility to randomize by surgeon.

3. Study Overview

The Study is designed to compare the effectiveness of Near Infrared Fluorescence Cholangiography (NIFC) to standard white light imaging (WLI) in visualizing and identifying the main biliary and hepatic structures (Cystic Duct, Right Hepatic Duct, Common Hepatic Duct, Common Bile Duct, Cystic-CBD junction, Cystic-Gallbladder junction and any Accessory Ducts) during laparoscopic cholecystectomy.

4. Study Objectives

a. Primary Objective:

Demonstrate that NIFC performs better than standard white light (WLI) alone in visualizing and identifying extra-hepatobiliary structures (Cystic Duct, Right Hepatic Duct, Common Hepatic Duct, Common Bile Duct, Cystic-CBD junction, Cystic-Gallbladder junction, and any Accessory Ducts) before and after dissection during Laparoscopic Cholecystectomy (LC).

b. Secondary Objectives:

1. Demonstrate that NIFC is an effective teaching tool to assist students and residents present in the O.R. during the procedure to identify extra-hepatobiliary structures (before/after dissection).
2. Demonstrate that the Time to Clip, which is defined as the time from the moment Calot's Triangle is first visualized to when the clip is applied, is reduced when using NIFC vs WLI alone.
3. Compare the mean number of procedures that required Conversion to Open using NIFC vs WLI alone.
4. Compare the mean Volume of Bleeding using NIFC vs WLI alone.
5. Compare the Incidence rate of Bile Leakage from the liver bed using NIFC vs WLI alone.
6. Compare the Incidence rate of Bile Duct Injury (BDI) using NIFC vs WLI alone.
7. Compare the mean Surgeon Confidence Level using NIFC vs WLI alone.

5. Study Endpoints

a. Primary Endpoint:

Detection Rate (DR) of each particular extra-hepatobiliary structure during Laparoscopic Cholecystectomy (LC) defined as the total number of patients in which the particular structure is detected before and after dissection in that arm of the Study (WLI or NIFC), divided by the total number of patients in that arm. Extra-hepatobiliary structures to be included in this assessment: Cystic Duct, Right Hepatic Duct, Common Hepatic Duct, Common Bile Duct, Cystic-CBD junction, Cystic-Gallbladder junction, and any Accessory Ducts.

b. Secondary Endpoints:

1. The DR for students/residents only (apart from experienced surgeons), both before and after dissection.
2. Time to Clip
3. Incidence of Conversion to Open Surgery
4. Volume of Bleeding
5. Incidence of Bile Leakage from the liver bed
6. The mean Incidence of Bile Duct Injury (BDI)
7. Surgeon Confidence Level

6. Covariates

Besides the comparison of the outcomes in both study arms, we will conduct an exploratory analysis to identify potential effect modifiers. The following baseline variables will be considered:

1) Patient data:
   a) Age
   b) Gender
   c) BMI
2) Patient history/condition:
   a) obesity
   b) liver disease
   c) lithiasis
   d) surgery status (elective/urgent/emergent)
3) Intra-operative factors:
   a) amount of fat covering cystic artery
   b) amount of inflammation
   c) presences of adhesions / scar tissue
4) Surgeon expertise (resident/attendant)

7. Additional Observations (NIFC group only)

a. "Reflux Maneuver"

According to previous publications, in some cases the Cystic Duct may not be seen with NIFC because the Cystic Duct may not contain ICG at the time of viewing. In those cases, a "reflux maneuver" [defined as using an atraumatic laparoscopic instrument to push on the Common Bile Duct in order to move more of the ICG from the Common Bile Duct through the Cystic Duct into the Gallbladder – thereby increasing visualization of the Cystic-Gallbladder junction] can be performed.

We will evaluate the usefulness of the Reflux Maneuver to visualize the Cystic Duct.

8. Design

a. Study Population

Participants will include patients aged 18-years old and above selected for Laparoscopic Cholecystectomy (LC).

b. Setting(s)

Participants will be recruited by the Department of Surgery at the following study sites, all of which are recognized hepato-bilio-pancreatic surgery centers:

- Cleveland Clinic (Weston, FL, USA)

- Cleveland Clinic (Cleveland, OH, USA)
- Cedars-Sinai Medical Center (Los Angeles, CA, USA)
- Hospital de Clínicas José de San Martín (Buenos Aires, Argentina)
- Tokyo Medical University Hospital (Tokyo, Japan)
- Asklepios Westklinikum (Hamburg, Germany)
- University of Insurbia (Varese, Italy)
- Klinikum Südstadt Rostock (Rostock, Germany)
- Kliniken Essen-Mitte (Essen, Germany)

Surgeons trained in laparoscopic and hepato-bilio-pancreatic (HBP) surgery will participate in the study. Principal and Lead Site Investigators of this Protocol are seniors and recognized HBP surgeons. Additionally, junior surgeons will be involved in the study. When a resident is present in the OR, he/she will perform the procedure under the supervision of the senior surgeon.

c. Enrollment Process

Eligible patients will be identified through clinical and test evaluation. Eligibility will be verified by the patient's primary surgeon. The surgeon will determine the indication and date of the surgery. Once a patient is confirmed as eligible, the surgeon will introduce the study in detail. If after being introduced to the study and having had the opportunity to ask questions, the patient is willing to participate, he/she will be asked to review and sign the informed consent document (Appendix XXX).

Upon entry in the clinical trial patients will be randomly allocated to the intervention arm. Data will be collected at enrolment time, during surgery, at the end of surgery and one week after surgery.

d. Randomization Process

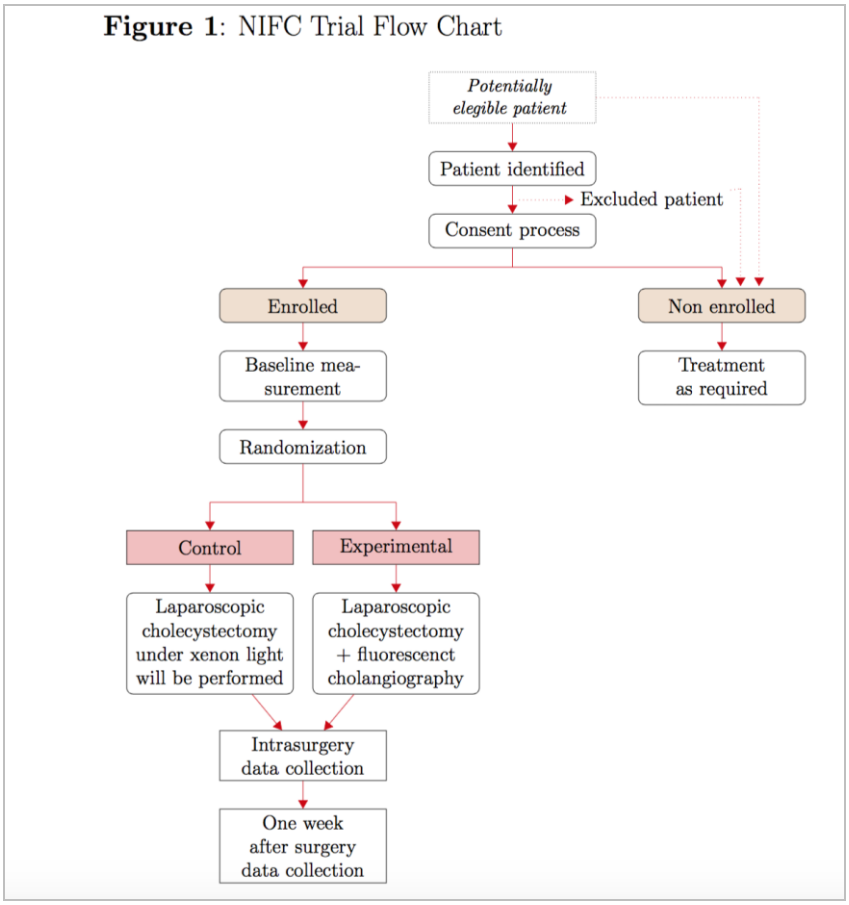
Upon entry in the clinical trial, the master study database (REDCap, described later in Section 16) will randomly allocated patients to one of the study arms (1:1) within site (1:1) using a computer generated random sequence. This will provide an allocation sequence for each site. Once a patient is enrolled and a database file in REDCap is initiated for that patient, he/she will be assigned electronically to one of the study arms.

Patient will be blind to the intervention but surgeon blinding will not be feasible due to the nature of the intervention. The study will involve a considerable number of surgeons in each site, which should compensate any potential bias of some of them in favor or against either approach.

e. Flow chart

Figure 1 shows the flow chart for the study, a multi-centered randomized controlled trial (RCT) 1:1 with two arms:

1. Control: WLI
   A laparoscopic cholecystectomy will be performed using Xenon white light imaging (WLI) only.
2. Experimental: NIFC
   A laparoscopic cholecystectomy will be performed using both white light imaging and near infrared light imaging with indocyanine green (ICG) intravenous dye.



9. Data collection and procedures

Data will be collected before, during and at the end of surgery; and one week after surgery.

a. Pre-Op data collection

i. Patient data

- Age
- Gender
- Weight
- Height
- BMI

ii. Patient clinical characteristics

- Liver disease
- Lithiasis
- Surgical status: elective/urgent/emergent

b. Intra-Op data collection

i. For NIFC arm only

- Time of ICC administration
- Was there any Adverse Reaction? If so, what happened and how was the patient treated?

ii. For both arms: PRIOR to dissection

- Categorize initial visualization
    - Amount of fat
    - Amount of inflammation
    - Presence of adhesions / scar tissue
- Remove the fat from the Calot's triangle area, retract the gallbladder and Hartmann's pouch
- Surgeon/Observer documents which extra-hepatic biliary structures are identified without doubt
- Start Dissection. Document the time hilar dissection was begun (baseline time)

iii. For both arms: AFTER dissection

- Surgeon/Observer documents which extra-hepatic biliary structures are identified without doubt
- Time to Clip: Document the time the Cystic Duct was clipped
- Volume of Bleeding
- Incidence of Bile Leakage
- Incidence of Anatomic Anomalies of the extra-hepatic biliary system, including any Accessory Ducts
- Incidence of performing IOC
- Incidence of CBD stones
- Incidence of Conversion to open surgery
- Incidence of Bile Duct Injury (BDI)?

iv. For NIFC arm only

- PRIOR to and AFTER DISSECTION: Surgeon/Observer documents which extra-hepatic biliary structures are identified without doubt using the "Reflux Maneuver" during NIFC
- Was the "reflux maneuver" useful?
- Surgeon preference: Was NIFC helpful?

c. One-week Post-Op data collection (usual control after surgery)

- Length of hospital stay

- Readmission?
- Complications?
    - Adverse drug reactions
    - Hemorrhage
    - Bile leak
    - Bile duct injury
- Death?

10. Subject Selection

a. Inclusion Criteria

1. Patients of both genders
2. Minimum age: 18 years old
3. Spoken and written command of the language spoken in the country's center
4. Ability to understand and follow the study procedures and sign the informed consent

b. Exclusion Criteria

1. Known allergies to iodides
2. Known history of cholangitis, pancreatitis, CBDS's, coagulopathy
3. Known liver disease
4. Women who are pregnant or breastfeeding, or for whom possibility of pregnancy was not ruled out

11. Study Device

a. Indocyanine Green (ICG) Fluorescent Dye

The drug used in these studies to evaluate the extra-hepatic bile duct is indocyanine green (ICG) and the equipment uses a wavelength around 800 nm (32,33,34,35,36,37). ICG, a cyanine dye, has been used in various medical diagnostic procedures since its FDA approval in 1956 (38).

ICG is a fluorophore responding to near-infrared irradiation that absorbs light between 790 and 805 nm, and re-emits it with an excitation wavelength of 835 nm. When given intravenously, ICG binds to plasma proteins and becomes confined to the intravascular space [15] . It is then exclusively metabolized by the liver and excreted by the biliary system 15 to 20 minutes after administration. These properties, in conjunction with the absence of any native biological fluorescence within these wavelengths, make ICG an ideal agent for the acquisition of high-quality images of the biliary tract.

b. Equipment

KARL STORZ (Tuttlingen, Germany) has developed a laparoscopic fluorescence imaging system that is suitable for both near-infrared fluorescence and xenon

(white) light imaging. During laparoscopic cholecystectomies, alternate exposure from xenon white light (STD mode) to near infrared light (ICG mode) is used to identify the biliary structures before, during and after dissection.

The fluorescent imaging system by KARL STORZ consists of a xenon light source (D-Light P) that can emit both near infrared (>780 nm) and white light, NIR-transmitting telescopes and a full HD 3-chip fluorescence imaging (FI) camera head capable of capturing both white light and NIR images. A foot pedal allows for a quick change between fluorescence and white light.

The *KARL STORZ Endoscopic ICG Imaging System* is comprised of the following components:

Model Number	Description
20133720-1	D-Light P light source
20010130	Foot switch
495 NCSC	Fiber optic light cable
26003 ACA/BCA	ICG endoscopes (0° and 30°)
TH102	Image1 SPIES H3-Z FI camera head
TC200 + TC300	Image1 SPIES camera control unit
n/a	Any medical-grade HD monitor with DVI-D or 3G-SDI input

c. Regulatory Status of Device

KARL STORZ has submitted a 510(k) to the FDA for this fluorescent imaging system [Appendix A, #K152583, submitted 9/10/15], but clearance has not yet been granted. As such, any clinical use requires IRB approval.

d. Rationale for Safe Use of the Device

The *KARL STORZ Endoscopic ICG Imaging System* is based on the same fluorescent imaging Principals using ICG as the FDA-approved *da Vinci® Firefly Surgical System* [510(k) #K124031, approval date September 13, 2013] produced by Intuitive Surgical, Inc. The man difference is the KARL STORZ system uses a filtered Xenon light source to produce the required NIR light, whereas the Intuitive device uses a laser diode.

It is the Principal Investigator's belief that the KARL STORZ imaging equipment does not pose significant risk to patients and therefore no Investigational Device Exemption (IDE) filing is required.

Each center will have available at least one KARL STORZ fluorescent imaging system.

12. Study procedures

a. Informed Consent

Prior to admission, the observer/resident/fellow/surgeon, from now on called "Researcher," will review the Informed Consent Form (Appendix B) with the patient and, if they desire to participate, both the patient and the Researcher will execute and dated the form.

b. Pre-Operative Case Report Form

At admission, the Researcher will complete a Pre-Operative Case Report Form (Appendix C) with baseline information abstracted from the patient chart.

c. Patient Randomization

Each surgeon will follow the standard laparoscopic surgical protocol of his/her center, and will comply with the following additional steps according to which arm of the study the patient is assigned:

i. Control arm (WLI only) procedures

1. After inserting the scope in the abdominal cavity, once other standard operatory procedures (e.g., taking down adhesions if necessary, or releasing scar tissue) are completed using white light imaging (WLI) only, the Researcher will record the time when Calot's triangle is first visualized. From this moment on, the surgery will be recorded.
2. After removing the fat from the gallbladder area, lifting the gallbladder over the liver, and grabbing the Hartman's pouch to visualize the Calot's triangle, but PRIOR TO DISSECTION, the Researcher will determine what extra-hepatic biliary structures can be specifically identified. Of note: because one of the goals of the Study is to evaluate NIFC as a teaching tool, residents and juniors should record what structures they were able to identify by themselves before any intervention of the attendant surgeon.
3. Then, AFTER DISSECTION, a similar assessment of what extra-hepatic biliary structures can be specifically identified using WLI only will be performed.
4. Anatomic anomalies of the biliary system will be documented on the case form and if an anatomic variation is found, a snap shot photo will be taken in addition to the video.
5. Immediately before clipping or proceeding with open surgery, the total time from Step 1 will be recorded, known herein as the "Time to Clip";

6. Before leaving the operation room, all participant surgeons and observers will complete the Intra-Operative Case Report Form (Appendices D and E, respectively).

ii. Experimental arm (NIFC) procedures

1. Patient randomized to the experimental arm, at least 45 mins before surgery, will receive a weight-scaled dose of indocyanine green (0.05 mg/kg) by IV and the time of administration and any adverse reactions will be recorded.
2. After inserting the scope in the abdominal cavity, once other standard operatory procedures (e.g., taking down adhesions if necessary, or releasing scar tissue) are completed using white light imaging (WLI) only, the Researcher will record the time when the Calot's triangle is first visualized. From this moment on, the surgery will be recorded.
3. After removing the fat from the gallbladder area, lifting the gallbladder over the liver, and grabbing the Hartman's pouch to visualize the Calot's triangle, but PRIOR TO DISSECTION, the Researcher will use NIFC to determine what extra-hepatic biliary structures can be specifically identified. This involves toggling the light source back and forth between STD mode (WLI) and ICG mode (NIFC). Of note: because one of the goals of the Study is to evaluate NIFC as a teaching tool, residents and juniors should record what structures they were able to identify by themselves before any intervention of the attendant surgeon.
4. Then, AFTER DISSECTION, a similar assessment of what extra-hepatic biliary structures can be specifically identified using NIFC will be performed.
5. Anatomic anomalies of the biliary system will be documented on the case form and if an anatomic variation is found, a snap shot photo will be taken in addition to the video.
6. Immediately before clipping or proceeding with open surgery, the total time from Step 1 will be recorded, known herein as the "Time to Clip";
7. Before leaving the operation room, all participant surgeons and observers will complete the Intra-Operative Case Report Form (Appendices D and E, respectively).

d. Post-Operative Case Report Form

During the standard follow-up exam, typically 7-10 day post-op, the Researcher will complete the Post-Operative Case Report Form (Appendix F).

e. Bile Duct Injury Form (if needed)

If the procedure results in a bile duct injury, the operating surgeon will complete the ancillary Bile Duct Injury Form (Appendix G).

13. Statistical Plan

a. Sample size

We estimate that the six participant centers will be able to enroll a minimum of 1000 patients in a 12 months period. Table XX shows the minimum effect size (increase in the rate of detection) that we will be able to detect with a 90% power or more, 5% level of significance, one-side test, when the detection rate in the control group are the ones indicated in the first column.

	Before dissection		After dissection	
Structure	DR control group	DR increase (effect size)	DR control group	DR increase (effect size)
Cystic	50%	10%	100%	--
Right Hepatic Duct	40%	10%	80%	7%
Common Hepatic Duct	46%	10%	70%	8%
Common Bile Duct	46%	10%	96%	3%
Cystic-CBD junction	29%	9%	60%	9%
Cystic-Gallbladder junction	60%	9%	70%	8%
Accessory Ducts	1%	3%	2%	4%

Regarding the main secondary outcome, incidence of injuries, the power to detect a drop from 8/1000 in the control arm to 2/1000 in the intervention arm, with a sample size of 500 patients per arm is 15%. Regretfully, with an achievable sample size as the one proposed above, the study will not have enough power to detect a drop in the incidence as important as the one considered.

b. Data Analysis

In general, descriptive statistics including frequencies and means will be used to characterize patient's baseline characteristics in both study arms. Analyses are designed to test the following hypotheses based on the primary objectives: Compared to those in the control arm, surgeons using NIFC will be able to identify a) more frequently the gallbladder cystic union (both before dissection and before clipping); b) a larger number of hepato-biliary structures and; c) more frequently some of the five hepato-biliary structures. We will test the first hypothesis using the chi-square test, the second one using non-parametric test (e.g. Kruskal-Wallis) and the third one using generalized mixed or hierarchical models to account for the clustering induced by the patient.

Regression models (logistic or generalized mixed models) will be fitted including covariates to evaluate if the effect of NIFC on the primary outcomes is modified by the patient's or surgeon's characteristics and site.

Regarding secondary outcomes we will use the Fisher's exact test or Chi square test (as needed) to compare proportion of patients with bile duct injury, open surgery or bleeding. Time to clipping and time to end of surgery will be compared between arms using the Kruskal-Wallis' test. Regression models will be used when possible -we expect very low incidence of injuries and open surgeries- to evaluate patient's and surgeon's effect modification.

Finally, for those outcomes specific for the NIFC group we will use logistic or generalized linear models to assess whether the reported helpfulness of the NIR light or the reflux maneuver is associated to patient's characteristics or surgeon's experience.

All statistical analysis will be conducted in R software.

14. Anticipated Problems and Solutions

a. Lower than expected Enrollment

If necessary, and if agreed upon by KARL STORZ, the enrollment period will be extended to reach the proposed 1,000 patients.

b. Approaches to Missing Data

We do not expect missing data for the main outcome as this information will be collected immediately after or during the surgery. Some of the secondary outcomes will be collected in a very short follow up period (7-10 days); we have however considered the alternative of phone calls to recover information in those patients not attending to clinic after surgery. Missing data on covariates are not expected either, as they are routine laboratory tests and studies.

15. Safety and Adverse Effects

a. Risks and Benefits

The dye may cause a feeling of warmth for several minutes following the injection. It may cause a change in the color of the stool (green). Uncommon allergic reactions include itchy skin and hives. Rare more severe allergic reactions such as wheezing, difficulty breathing, and low blood pressure may occur.

There is no personal benefit by participating in this research study. The increased visualization of the extra-hepatobiliary anatomy may aid the surgeon.

The knowledge to be gained from this research may be beneficial for other patients, society or science.

b. Potential Risks

Potential risks are similar to routine laparoscopic cholecystectomy, including possible bile duct injury, bleeding, and/or conversion to open surgery.

Drug related adverse complications may be due to allergic reactions.

c. Procedure to Minimize Risk

Administration and dose of ICG will be confirmed and performed only by trained medical personnel. During the surgical procedure, the patient will be closely monitored by the operating room staff.

d. Potential Benefits

The increased visualization of the extra-hepatic biliary anatomy may aid the surgeon.

The knowledge to be gained from this research may be beneficial for other patients, society or science.

16. Data Handling and Record keeping (REDCap)

a. Overview

The medical and research information recorded about the patient for this research will be used within the Institution and/or disclosed outside the Institution as part of this multi-center study. The procedure done solely for this research study may be placed in the medical record to indicate the patient's participation in this study.

The information recorded about the patient as part of this research will be maintained in a confidential manner.

Federal regulations require that the patient authorize the release of any health information that may reveal patient identity. The results of this research may be presented at meetings or in publications; however, Patient identity will not be disclosed in any presentation.

The Institution will not use or disclose the information collected in this study for another research purpose without patient written permission, unless the Institution's Institutional Review Board (IRB) gives permission after ensuring that appropriate privacy safeguards are in place.

b. The data will be safely uploaded in REDCap

REDCap (**Research Electronic Data Capture**) is a mature, secure web application for building and managing online surveys and databases. While REDCap can be used to collect virtually any type of data, it is specifically geared to support data capture for research studies. The REDCap Consortium is composed of 1,589 active institutional partners in 92 countries who utilize and support REDCap in various ways

Using REDCap's stream-lined process for rapidly developing projects, we will be able to create and design this project using 1) the online method from our web browser using the Online Designer; and/or 2) the offline method by constructing a 'data dictionary' template file in Microsoft Excel, which can be later uploaded into REDCap. Both surveys and databases (or a mixture of the two) are going to be be built using these methods. REDCap provides audit trails for tracking data manipulation and user activity, as well as automated export procedures for seamless data downloads to Excel, PDF, and common statistical packages (SPSS, SAS, Stata, R).

17. Responsibilities

a. Principal Investigator (PI)

The Principal Investigator (PI) leads the team that conducts the clinical trial and is ultimately accountable for its conduct. The PI's responsibilities include:

- Designing, conducting and monitoring the Protocol
- Recruiting Lead Site Investigators at the various clinical sites to participate in the Multi-Center Study according to the Protocol
- Overseeing the integrity and analysis of research data collected during the Study
- Ensuring that the Protocol is followed by the various sites and that data are collected promptly and accurately
- Ensuring that subject's rights, safety, and welfare are protected
- Informing and educating Lead Site Investigators of their role in the multi-center Study
- Assisting, as needed, to help train personnel at the various Sites about their role in the Study
- Gathering aggregate data from the Sites
- Summarizing the results of the Study, with the assistance of a biostatistician
- Publishing the results of the Study as lead author, with reference to the other Lead Site Investigators

b. Lead Site Investigator (LSI)

The Lead Site Investigator (LSI) is responsible for the day-to-day activities at his/her particular site to conduct the Study according to the Protocol. The LSI's responsibilities include:

- Overseeing the informed consent process
- Educating research participants and other staff of their role in the Study according to the Protocol
- Ensuring necessary approvals are obtained
- Recruiting, screening and scheduling patient procedures

- Implementing Study requirements
- Maintaining the integrity of the Protocol, including the research data collected
- Documenting patient information, protocol deviations/violations, and regulatory compliance based on their own IRB requirements
- Providing records for inspection
- Complying with record-keeping and record-retention requirements

c. Clinical Data Manager (CDM)

The Clinical Data Manager at each site is responsible for organizing and collecting the data per the requirements outlined in the Protocol including:

- Collecting source documents before, during, and after each Study procedure, including
    - Informed Consent Forms
    - Case Report Forms (Pre-op, Intra-op, and Post-op)
    - Video and Still recordings from the procedure
- Inputting the data into the general Study REDCap database (as described in Section 17.b above.

d. Study Monitoring, Auditing and Inspecting

The conduct of the study will be monitored by representatives of Karl Storz (William Schnorr)and the Global Coordinator (Raul Rosenthal and Fernando Dip) to ensure compliance with the protocol, GCP, ICH and applicable regulations. The coordinator will have regular contacts with the study centers, including remote access to provide information and support to the investigator(s) and confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the RedCap.

The coordinator will perform source data verification (SDV) (a comparison of the data in the RedCap with the patient's medical records and other records relevant to the study including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).

The Investigator must ensure that clinical study records are retained according to national regulations, as documented in the clinical trial agreement entered into with the Sponsor in connection with this study. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution, or private practice. The Investigator must inform The Main Center (Cleveland clinic Florida) immediately if any documents are to be destroyed, to be transferred to a different facility, or to be transferred to a different owner.

The co- investigators will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and

Institutional compliance and quality assurance groups of all study related documents (for example, source documents, regulatory documents, data collection instruments, study data etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Institutional compliance and quality assurance offices."

18. Publication Plan

The parties, recognizing the importance of communicating clinical trial results to the public and to the medical and scientific communities in an accurate and complete manner, intend for the first Publication of the Study to include the results from all of the study centers and to appear in a peer-reviewed scientific journal, in accordance with the Protocol.

Without the prior written agreement of the Principal Investigator and KARL STORZ, Institution shall not Publish or submit for Publication, directly or indirectly, any Manuscript prior to the publication of an article in a peer-reviewed scientific journal summarizing the data generated by all of the study centers, unless no such article is so published before the first anniversary of the finalization of the multi-center database, in which case Institution may Publish or submit for Publication a Manuscript without further delay.

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20. Appendices

a. 510(k) Acknowledgement Letter from FDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES — Public Health Service

Acknowledgment Letter

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

09/10/2015

Mike Samuels
Regulatory Affairs Specialist
KARL STORZ ENDOSCOPY-AMERICA, INC.
2151 E. GRAND AVENUE
EL SEGUNDO, CA 90245
United States

Dear Mike Samuels:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has received your submission. This submission has been assigned the unique document control number below. Please refer prominently to this number in all future correspondence that relates to this submission. Failure to do so may result in processing delays. If the 'Applicant' identified below is incorrect, please notify the 510(k) Staff immediately at (301) 796-5640.

Submission Number: K152583
Received: 09/10/2015
Applicant: KARL STORZ ENDOSCOPY-AMERICA, INC.
Device: KARL STORZ Endoscopic ICG Imaging System

We will notify you when the processing of your 510(k) has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

If any additional information is required, we will notify you via an Acceptance Review communication, Additional Information (AI) request, and/or Interactive Review communication. For additional information on these types of communication and their effect on the FDA Review Clock (if any), please refer to the following guidance documents:

"FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Goals" at
http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm089735.htm.

"Refuse to Accept Policy for 510(k)s" at
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM315014.pdf.

"Types of Communication During the Review of Medical Device Submissions" at
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm341918.htm.

When responding to an information request that stops the FDA Review Clock (e.g., an AI request or refuse to accept (RTA) decision), you must submit your complete response with valid electronic copy (eCopy) to the Document Control Center (DCC) at the above address. An incomplete response or a response sent any other way (e.g., to another address or via email) will **not** be considered an official response and will not restart the FDA Review Clock. For more information about FDA's eCopy program, including the new technical standards for an eCopy, refer to the guidance document, "eCopy Program for Medical Device Submissions" at
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf

To learn more about the overall 510(k) submission process, please refer to our website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm.

If you have any procedural or policy questions, please refer to our website at http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm or contact the Division of Industry and Consumer Education (DICE) at its toll-free number (800) 638-2041, (301) 796-7100, or *DICE@fda.hhs.gov*.

Sincerely yours,

Marjorie Shulman
Director, 510(k) Program
Premarket Notification (510(k)) Staff
Office of Device Evaluation
Center for Devices and Radiological Health

b. Patient Informed Consent Form

Near Infrared Incisionless Fluorescent Cholangiography (NIFC)
INFORMED CONSENT FORM

Multi-Center Reasearch Study Title: Efficacy Of Near Infrared Incisionless Fluorescent Cholangiography (NIFC) During Laparoscopic Cholecystectomy

General:
Principal Investigator: Fernando Dip, MD
Sponsor: Cleveland Clinic Florida (Weston, FL, USA)
Collaborator: KARL STORZ GMBH & Co KG

Local:
Your Institution: _____ **Street Address**: _____
Lead Site Investigator: _____ **City**: _____ **State**: ___ **Zip**: _____
Contact Phone Number (office): _____

Carefully review this consent document. The purpose of a consent document is to provide you with information to help you decide whether you wish to participate in research. Your decision is completely voluntary and will not affect your medical care if you choose not to participate. It is important for you to ask questions and understand the research risks, benefits and alternatives.

Please note:

- You are being asked to participate in a research study
- Carefully consider the risks, benefits and alternatives of the research
- Your decision to participate is completely voluntary

Your doctor may be an investigator in this research study, and as a research investigator, is interested in both your welfare and in the conduct of the research study. Before entering this study or at any time during this research, you may ask for a second opinion about your care from another doctor who is not involved with the research study. You are not under any obligation to participate in any research project offered by your doctor.

1. INFORMATION ON THE RESEARCH

Why Are You Being Asked To Take Part In This Research?

You are being asked to participate in this research study because you will be undergoing a Cholecystectomy.

Why Is This Study Being Done?

To perform a cholecystectomy, it is necessary to identify the biliary structures that connect to the gallbladder prior to its removal, and these extrahepatic biliary structures can be difficult to identify in some cases. The purpose of this study is to evaluate the accuracy of the use of a new technology and technique called near-infrared fluorescent cholangiography (NIFC) and how this technique could improve the identification of extrahepatic biliary structures compared to the standard technique of using white light alone.

How Many People Will Take Part In The Study?

This is an international multi-center trial and about 1,000 people total will take part in this study across the participating centers.

What Is Involved In The Study?

This study will compare the use of the normal laparoscopic (white) light to a new technique using near-infrared fluorescence to visualize the biliary anatomy during cholecystectomy. This will be done by using a new imaging system (manfactured by KARL STORZ) and a fluorescent dye (ICG) that has been used in medicine and approved by the FDA since 1959.

One dose of the dye will be given to you through your IV line one hour before your surgery in order to evaluate the bile ducts. There is nothing in addition for you to do, as the test will compare the visibility this technology provides to your surgeon during the procedure.

MULTICENTER NIFC STUDY Page 1 of 3 ICF v1.0

Near Infrared Incisionless Fluorescent Cholangiography (NIFC)
INFORMED CONSENT FORM

How Long Will You Be In The Study?

Your participation in this study will last the length of your surgical procedure only.

2. RISKS AND DISCOMFORTS

What Are The Risks Of The Study?

IndoCyanine Green (ICG) dye will be used during this study, which may cause discolored stool (green), and some cases headache, itchy skin, hives, and sweating. If you have a known allergy to iodides, you should not participate in this study.

3. BENEFITS

Are There Benefits To Taking Part In The Study?

There is no personal benefit to you by participating in this research study. The increased visualization of the operative area (bile ducts) may help your the surgeon during the procedure.

Due to Randomization in this study, half of the participants will be in the Control group and as such, you may not receive the ICG and your operation will proceed using standard white light only.

The knowledge to be gained from this research may be beneficial for other patients, society or science.

4. ALTERNATIVES

What Other Options Are There?

There are no options, and the alternative is not to participate in this study, in which case your surgery will be conducted as per the standard method.

5. PRIVACY AND CONFIDENTIALITY

The medical and research information recorded for this study will be used within and/or disclosed outside your Institution as part of the Multi-Center Study. Tests and procedures done solely for this research study may be placed in your medical record to indicate your participation in this study.

The information recorded about you, as part of this research will be maintained in a confidential manner. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Upon completion of the study, you may have access to the research information if contained in the medical record. During the study, your access to research information about you will be limited.

Preventing this access during the study keeps the knowledge of study results from affecting the reliability of the study. This information will be available should an emergency arise that would require your treating physician to know this information to assist in treating you.

Federal regulations require that you authorize the release of any health information that may reveal your identity. The persons and entities that you are authorizing to use or disclose your individually identifiable health information may include the study doctor, the study staff, Institution monitors/auditors and IRB, the study Collaborator and its agents, the U.S. Food and DrugAdministration (FDA), the Department of Health and Human Services (DHHS), other governmental agencies from foreign countries. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. The Institution also may use and disclose this information for treatment and payment reasons. The Institution must comply with legal requirements that mandate disclosure in unusual situations. Once your personal health information is released, it may be re-disclosed and no longer protected by federal privacy laws. The results of this research may be presented at meetings or in publications; however, your identity will not be disclosed in those presentations.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by contacting the Lead Site Investigator at your Institution. If you do so, your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of the research. In addition, information already disclosed outside the Institution cannot be retrieved. Even if you ask us to stop outside disclosures, information collected about you will be disclosed as required by state and federal law.

Near Infrared Incisionless Fluorescent Cholangiography (NIFC)
INFORMED CONSENT FORM

The Institution will not use or disclose the information collected in this study for another research purpose without your written permission, unless the Institution Institutional Review Board gives permission after ensuring that appropriate privacy safeguards are in place. The Institutional Review Board is a committee whose job is to protect the safety and welfare of research subjects.

By signing this Informed Consent Form, you are authorizing such access to your medical records. If you choose not to sign this consent form, you will not be permitted to participate in this research study.

6. COSTS

There are no additional costs to you for participation in this research study. The cost for routine tests and services that would normally be performed even if you do not participate in the study will be billed to you or your insurance provider. You will be responsible for all co-pays and deductibles.

7. VOLUNTARY PARTICIPATION

What Are Your Rights As A Participant?

Taking part in this study is voluntary. You will be told of any new, relevant information from the research that may affect your health, welfare, or willingness to continue in this study. You may choose not to take part or may leave the study at any time. Withdrawing from the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to withdraw from the study, you should discuss with your study doctor your decision to ensure a safe withdrawal.

8. QUESTIONS

Whom Do You Call With Questions Or Problems?

If you have any questions, concerns or complaints about the research, or develop a research-related problem, contact Lead Site Investigator at your Institution or call your Institution after business hours, and ask to talk with the Resident for General Surgery On-Call. If you have questions about your rights as a research subject, you should contact the Institutional Review Board at your Institution.

9. SIGNATURE

Statement of Participant

I have read and it has been verbally explained to me the above information, and I have had all my questions answered to my satisfaction. I understand that my participation is voluntary and that I may stop my participation in the study at any time. Signing this form does not waive any of my legal rights. I understand that a copy of this consent will be provided to me. By signing below, I agree to take part in this research study.

_____	_____	_____
Printed Name of Participant	Participant Signature	Date

Statement of Person Conducting Informed Consent Discussion

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

_____	_____	_____
Printed Name of Person Conducting Consent	Signature of Person Conducting Consent	Date

c. Pre-Op Case Report Form

Near Infrared Incisionless Fluorescent Cholangiography (NIFC)

PRE-OPERATIVE CASE REPORT FORM

INSTITUTION: _____ PATIENT ID: _____ PROCEDURE DATE: _____

NAME OF PERSON COMPLETING FORM: _____

PATIENT INFORMATION:

Age: _____ Sex: M F Height: _____ Weight: _____ BMI: _____

Known allergy to Iodides? No ☐ Yes ☐ If yes, **EXCLUDE FROM STUDY!!**

Liver Disease? No ☐ Yes ☐ If yes, what type? ☐ Cirrhosis ☐ fatty liver ☐ other: _____

LABORATORY TESTS (within 15 days prior to surgery date):

PREGNANCY TEST? ☐ Negative ☐ Not Done

IMAGING STUDIES:

- LITHIASIS? No ☐ Yes ☐ If Yes,

  Diagnosed by: ☐ Ultrasound ☐ CT Scan ☐ MRCP ☐ EUS ☐ ERCP

- ERCP/ES? No ☐ Yes ☐ If Yes,

  Date performed: _____ Stones in Bile Duct? No ☐ Yes ☐

  SPHINCHTEROTOMY performed? No ☐ Yes ☐

SURGERY STATUS: ☐ Elective ☐ Urgent ☐ Emergency

MULTICENTER TRIAL Page 1 of 1 PREOP-CRF v1.0

d. Intra-Op Case Report Form – Surgeon

Near Infrared Incisionless Fluorescent Cholangiography (NIFC)

INTRA-OPERATIVE CASE REPORT FORM - PERFORMING SURGEON

INSTITUTION: _____ PATIENT ID: _____ PROCEDURE DATE: _____

SURGEON NAME: _____ _____
(PRINT) (SIGNATURE)

ACADEMIC TITLE: _____ Years in practice: _____ Approx. #Lap Choles Performed: _____

STUDY ARM: ☐ **WLI** (STD mode on light source only) ☐ **NIFC** (using both STD and ICG modes)

1. **For NIFC group only:**
   - Time of ICG Administration: _____ AM / PM
   - Was there an Adverse Reaction to the ICG? Yes ☐ No ☐
     If Yes, how was it detected? _____
     _____
     If Yes, how was it managed? _____
     _____

2. **PRE-DISSECTION**

A. Categorize the initial visualization:
   - Amount of fat: Can you see the Cystic Artery? ☐ Yes ☐ No
   - Level of inflammation: ☐ Minimal ☐ Moderate ☐ Significant
   - Were adhesions and/or scar tissue needed to be removed prior to visualization? ☐ Yes ☐ No

B. Remove the fat from the Calot's triangle area, retract the gallbladder and Hartmann's pouch.

C. Document visualization of extra-hepatic biliary anatomy:

For both arms, scope the Calot's triangle area using STD (white-light) mode. If in the NIFC arm, toggle between STD and ICG modes on light source as needed. Check the appropriate boxes below based on what is visible:

Time of Initial Visualization: _____ AM / PM

	Yes	Maybe	No
Cystic Duct	☐	☐	☐
Right Hepatic Duct	☐	☐	☐
Common Hepatic Duct	☐	☐	☐
Common Bile Duct (CBD)	☐	☐	☐
Cystic-CBD junction	☐	☐	☐
Cystic-Gallbladder junction	☐	☐	☐
Accessory Ducts	☐	☐	☐

D. **For NIFC Arm Only:** "Reflux Maneuver" Attempted? ☐ Yes ☐ No

If the Cystic Duct cannot be visualized with fluorescence, use an atraumatic laparoscopic instrument to push on the Common Bile Duct in order to move more of the ICG from the Common Bile Duct through the Cystic Duct into the Gallbladder – thereby increasing visualization of the Cystic Duct - Gallbladder Union. Check the appropriate boxes based on what is visible:

	Yes	Maybe	No
Cystic Duct	☐	☐	☐
Cystic-CBD junction	☐	☐	☐
Cystic-Gallbladder junction	☐	☐	☐

MULTICENTER TRIAL Page 1 of 2 SURG-CRF v1.0

Near Infrared Incisionless Fluorescent Cholangiography (NIFC)

INTRA-OPERATIVE CASE REPORT FORM - PERFORMING SURGEON

START DISSECTION: **Time of hilar dissection:** _____ AM / PM

3. AFTER-DISSECTION

A. Document visualization of extra-hepatic biliary anatomy:

For both arms, scope the Calot's triangle area using STD (white-light) mode. If in the NIFC arm, toggle between STD and ICG modes on light source as needed. Check the appropriate boxes below based on what is visible:

	Yes	Maybe	No
Cystic Duct	☐	☐	☐
Right Hepatic Duct	☐	☐	☐
Common Hepatic Duct	☐	☐	☐
Common Bile Duct (CBD)	☐	☐	☐
Cystic-CBD junction	☐	☐	☐
Cystic-Gallbladder junction	☐	☐	☐
Accessory Ducts	☐	☐	☐

B. For NIFC Arm Only: "Reflux Maneuver" Attempted? ☐ Yes ☐ No

Repeat the Reflux Maneuver. Check the appropriate boxes based on what is visible:

	Yes	Maybe	No
Cystic Duct	☐	☐	☐
Cystic-CBD junction	☐	☐	☐
Cystic-Gallbladder junction	☐	☐	☐

4. **Time to Clip:** Time the Cystic Duct was clipped: _____ AM / PM

5. **Volume of Bleeding:** _____ mL in the bucket/bag or from anesthesia chart at the conclusion of the procedure

6. **Bile Leakage:** No ☐ Yes ☐ If yes, ☐ Liver bed ☐ Other:_____ Did NIFC help identify leak? Yes ☐ No ☐

7. **Anatomic Anomalies:** No ☐ Yes ☐ If yes, describe: _____

If yes, do you feel NIFC helped you identify this anomaly? Yes ☐ No ☐ N/A (WLI arm) ☐

8. **Was IOC performed?** Yes ☐ No ☐

9. **Were CBD Stones present?** Yes ☐ No ☐ Not Checked ☐

10. **Was the procedure converted to Open?** Yes ☐ No ☐

If yes, explain why? _____

_____

11. **Was there a Bile Duct Injury (BDI) during the surgery?** Yes ☐ No ☐

If yes, complete the BDI Form as described in the Study Protocol.

12. SURGEON FEEDBACK after NIFC:

Did you feel NIFC made your procedure SAFER? Yes ☐ No ☐

Were you more CONFIDENT using NIFC vs WLI alone? Yes ☐ No ☐

Would you PREFER to use NIFC again vs WLI alone? Yes ☐ No ☐

MULTICENTER TRIAL Page 2 of 2 SURG-CRF v1.0

e. Intra-Op Case Report Form – Observer

Near Infrared Incisionless Fluorescent Cholangiography (NIFC)

INTRA-OPERATIVE CASE REPORT FORM - OBSERVER

INSTITUTION: _____ PATIENT ID: _____

SURGERY PERFORMED BY: _____ PROCEDURE DATE: _____

OBSERVER NAME: _____ _____
(PRINT) (SIGNATURE)

EXPERIENCE LEVEL OF PERSON COMPLETING FORM:

☐ ATTENDING (Years in practice ___) ☐ FELLOW ☐ RESIDENT (YR___) ☐ MEDICAL STUDENT (YR___)

ACADEMIC TITLE: _____ Approximate # of Lap Choles Performed: _____

STUDY ARM: ☐ **WLI** (STD mode on light source only) ☐ **NIFC** (using both STD and ICG modes)

1. **PRE-DISSECTION**

A. Remove the fat from the Calot's triangle area, retract the gallbladder and Hartmann's pouch.

B. **Document visualization of extra-hepatic biliary anatomy:**
For both arms, scope the Calot's triangle area using STD (white-light) mode. If in the NIFC arm, toggle between STD and ICG modes on light source as needed. Check the appropriate boxes below based on what is visible:

	Yes	Maybe	No
Cystic Duct	☐	☐	☐
Right Hepatic Duct	☐	☐	☐
Common Hepatic Duct	☐	☐	☐
Common Bile Duct (CBD)	☐	☐	☐
Cystic-CBD junction	☐	☐	☐
Cystic-Gallbladder junction	☐	☐	☐
Accessory Ducts	☐	☐	☐

C. For NIFC Arm Only: **REFLUX MANEUVER**
If the Cystic Duct cannot be visualized with fluorescence, use an atraumatic laparoscopic instrument to push on the Common Bile Duct in order to move more of the ICG from the Common Bile Duct through the Cystic Duct into the Gallbladder – thereby increasing visualization of the Cystic Duct - Gallbladder Union. Check the appropriate boxes based on what is visible:

	Yes	Maybe	No
Cystic Duct	☐	☐	☐
Cystic-CBD junction	☐	☐	☐
Cystic-Gallbladder junction	☐	☐	☐

MULTICENTER TRIAL Page **1** of **2** OBS-CRF v1.0

Near Infrared Incisionless Fluorescent Cholangiography (NIFC)

INTRA-OPERATIVE CASE REPORT FORM - OBSERVER

2. AFTER-DISSECTION

A. Document visualization of extra-hepatic biliary anatomy:
For both arms, scope the Calot's triangle area using STD (white-light) mode. If in the NIFC arm, toggle between STD and ICG modes on light source as needed. Check the appropriate boxes below based on what is visible:

	Yes	Maybe	No
Cystic Duct	☐	☐	☐
Right Hepatic Duct	☐	☐	☐
Common Hepatic Duct	☐	☐	☐
Common Bile Duct (CBD)	☐	☐	☐
Cystic-CBD junction	☐	☐	☐
Cystic-Gallbladder junction	☐	☐	☐
Accessory Ducts	☐	☐	☐

B. For NIFC Arm Only: Repeat the Reflux Maneuver. Check the appropriate boxes based on what is visible:

	Yes	Maybe	No
Cystic Duct	☐	☐	☐
Cystic-CBD junction	☐	☐	☐
Cystic-Gallbladder junction	☐	☐	☐

MULTICENTER TRIAL Page 2 of 2 OBS-CRF v1.0

f. Post-op Case Report Form

Near Infrared Incisionless Fluorescent Cholangiography (NIFC) 1

POST-OPERATIVE FORM

INSTITUTION: _____ PATIENT ID: _____ PROCEDURE DATE: _____

FORM COMPLETED BY: _____ FORM COMPLETION DATE: _____
(PRINT)

1. Length of hospital stay: _____ (days)
2. Was patient readmitted: No ☐ Yes ☐ If Yes, complete the following:
   a. Days after discharge: ____ (NOTE: Day of Surgery is Day "0")
   b. Reason for readmission: _____
   c. Treatment administered: _____
   d. Length of stay: _____ (days)
3. Death (30 d): No ☐ Yes ☐ If Yes, cause of death: _____
4. Complications: No ☐ If No, you have completed this form. Yes ☐ If Yes, please continue…
   a. Indocyanine green drug reactions: No ☐ If No, skip to surgical complications. Yes ☐ If Yes, continue
      i. Flushing? No ☐ Yes ☐ If yes, please complete:
         1. Treatment required? No ☐ Yes ☐
         2. If Yes, what treatment: _____
      ii. Urticaria? No ☐ Yes ☐ If yes, please complete:
         1. Treatment required? No ☐ Yes ☐
         2. If Yes, what treatment: _____
      iii. Other possible drug reaction? No ☐ Yes ☐ If Yes, please complete:
         1. Describe: _____
         2. Onset (day of surgery is "0"): _____
         3. Duration (Hours): _____
         4. Treatment required? No ☐ Yes ☐
         5. If Yes, what treatment: _____

MULTICENTER TRIAL Page 1 of 2 POSTOP-CRF v1.0

Near Infrared Incisionless Fluorescent Cholangiography (NIFC) 2

POST-OPERATIVE FORM

b. Hemorrhage? No ☐ Yes ☐ If Yes, please complete:
   i. ...requiring transfusion? No ☐ Yes ☐
   ii. ...requiring re-operation? No ☐ Yes ☐
   iii. ...requiring longer hospitalization? No ☐ Yes ☐
c. Intra-abdominal pain in right upper quadrant? No ☐ Yes ☐
d. Bile leak (without bile duct injury)? No ☐ Yes ☐ If Yes, please complete:
   i. ...requiring percutaneous drainage? No ☐ Yes ☐
   ii. ...requiring reoperation? No ☐ Yes ☐
   iii. ...treated with percutaneous drainage only? No ☐ Yes ☐
   iv. ...treated with transpapillary stent? No ☐ Yes ☐
   v. ...treated with percutaneous drainage and transpapillary stent? No ☐ Yes ☐
   vi. Source of leak:
      1. cystic duct stump leak? No ☐ Yes ☐
      2. liver bed? No ☐ Yes ☐
      3. never determined? No ☐ Yes ☐
e. Bile duct injury? No ☐ Yes ☐ If Yes, complete separate BDI form

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g. Bile Duct Injury (BDI) Form

Near Infrared Incisionless Fluorescent Cholangiography (NIFC)

BILE DUCT INJURY FORM

INSTITUTION: _____ PATIENT ID: _____ PROCEDURE DATE: _____

FORM COMPLETED BY: _____ FORM COMPLETION DATE: _____
(PRINT)

1. How was the injury recognized? ☐ Intraoperatively. Go to #2 ☐ Postoperatively. Go to #3

2. Intraoperative information:
   a. Bile leak? No ☐ Yes ☐ If Yes, where?
      i. ☐ Cystic duct
      ii. ☐ Common bile duct
      iii. ☐ Common hepatic duct
      iv. ☐ Right hepatic duct
      v. ☐ Left hepatic duct
      vi. ☐ Small accessory duct
      vii. ☐ Liver bed
      viii. ☐ Couldn't tell
      ix. ☐ Other. Please specify:_____
   b. Could the cut end of the tubular structure be seen? No ☐ Yes ☐
   c. Partial or complete occlusion? No ☐ Yes ☐ If Yes, what the mechanism caused the occlusion?
      i. ☐ Tie or clip at cystic common duct junction
      ii. ☐ Scissor
      iii. ☐ Cautery
      iv. ☐ Ultrasonic dissector
      v. ☐ Other. Please specify: _____

3. Postoperative information:
   a. Recognized postoperative day: _____ (day of operation is Day "0")
   b. Diagnosed or suspected by imaging? No ☐ If No, skip to #c Yes ☐ If Yes,
      i. ☐ MRCP
      ii. ☐ CT scan
      iii. ☐ Ultrasound
      iv. ☐ Hida scan

MULTICENTER TRIAL Page 1 of 3 BDI-CRF v1.0

Near Infrared Incisionless Fluorescent Cholangiography (NIFC)

BILE DUCT INJURY FORM

c. ERCP attempted/performed? No ☐ If No, skip to #d Yes ☐ If Yes,
   i. ☐ Unsuccessful
   ii. ☐ Injury identified
   iii. ☐ Injury stented
   iv. ☐ CBD stone in addition
   v. ☐ Other. Please specify: _____

d. Percutaneous transhepatic intervention performed? No ☐ If No, skip to next question Yes ☐ If Yes,
   i. ☐ Drainage of duct(s) only
   ii. ☐ Stent of duct(s)
   iii. ☐ Other. Please describe: _____

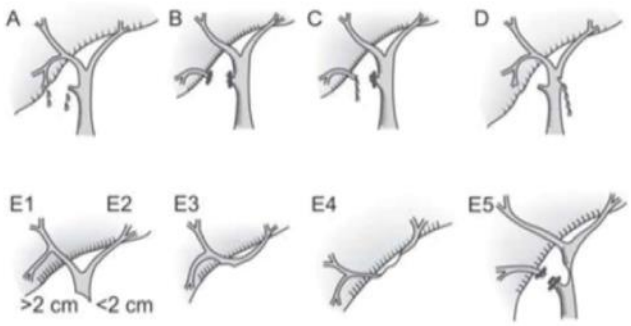
e. Percutaneous subhepatic drainage? No ☐ If No, skip to next question Yes ☐ If Yes,
   i. By CT scan
   ii. By ultrasound

4. Re-operation for injury? No ☐ If No, skip to next question Yes ☐ If Yes,
   a. Date of first reoperation: _____
   b. Number of days postoperative: _____ (Original lap chole surgery date is Day "0")
   c. Drain only? No ☐ Yes ☐
   d. Roux-en-y reconstruction? No ☐ Yes ☐
   e. T-tube placement? No ☐ Yes ☐
   f. End-to-end repair? No ☐ Yes ☐
   g. Other? No ☐ Yes ☐ If yes, please specify: _____
   h. Additional surgeries to treat bile duct injury? No ☐ Yes ☐ If yes, answer #a-g above, with the date of each reoperation on additional forms as needed.

Near Infrared Incisionless Fluorescent Cholangiography (NIFC)

BILE DUCT INJURY FORM

5. Classification of bile duct injury (per Strasberg-Bismuth):



- ☐ Type A: Cystic Duct leak or leak from small ducts in the liver bed
- ☐ Type B: Occlusion of a part of the biliary tree, usually an aberrant right hepatic duct
- ☐ Type C: Transection without ligation of an aberrant right hepatic duct
- ☐ Type D: Lateral injury to major bile duct
- ☐ Type E1: Transection >2cm from confluence
- ☐ Type E2: Transection <2cm from confluence
- ☐ Type E3: Transection in hilum
- ☐ Type E4: Separation of major ducts in hilum
- ☐ Type E5: Type C plus injury in hilum

6. Please attach to this form all operative reports, procedure reports, imaging and pathology reports from the original laparoscopic cholecystectomy to the most recent operation. Thank you.

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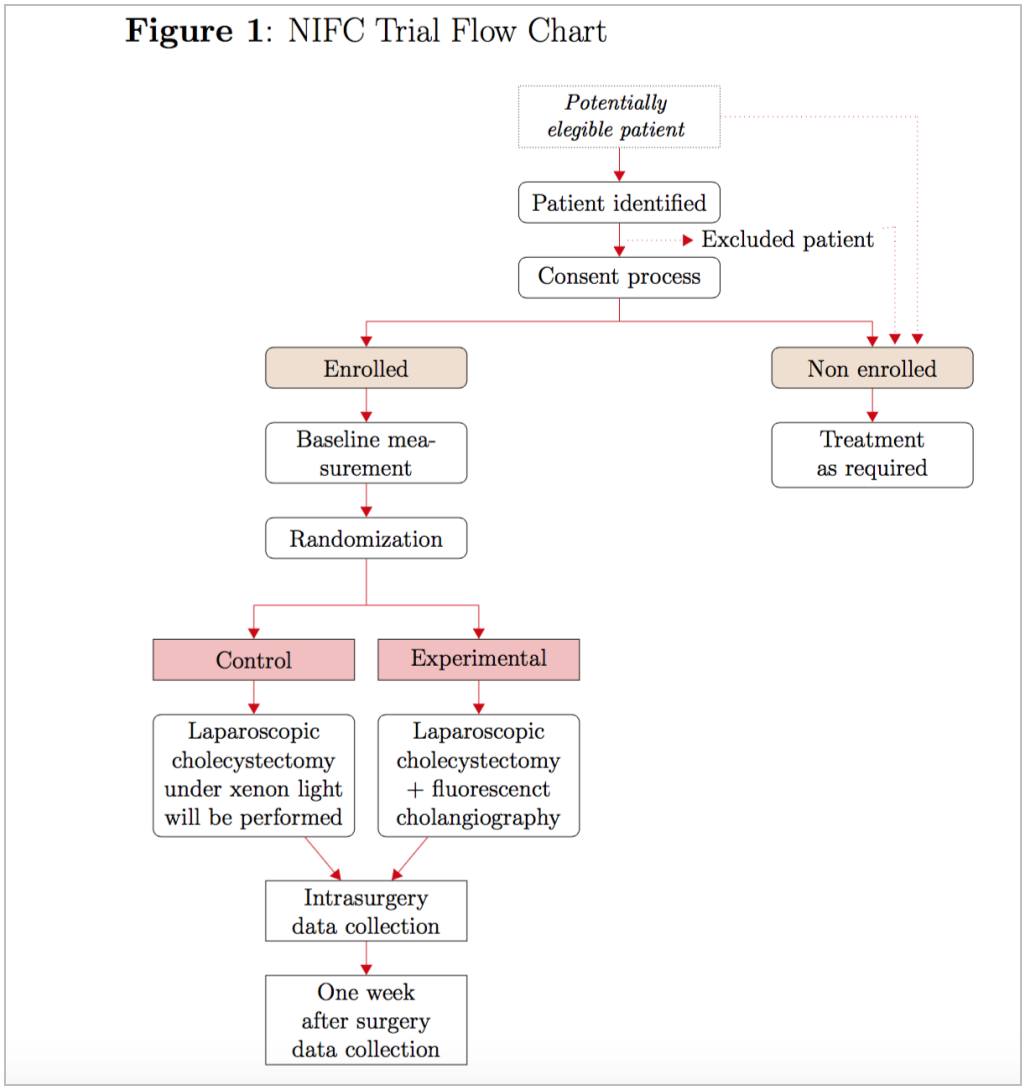
h. Schedule of events

(from **Section 8.f. Trial Flow**)



i. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:

- 29th WMA General Assembly, Tokyo, Japan, October 1975
- 35th WMA General Assembly, Venice, Italy, October 1983
- 41st WMA General Assembly, Hong Kong, September 1989
- 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
- 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
- 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
- 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
- 59th WMA General Assembly, Seoul, Republic of Korea, October 2008
- 64th WMA General Assembly, Fortaleza, Brazil, October 2013

i. Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical Principals for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these Principals.

ii. General Principals

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve

preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

iii. Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

iv. Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

v. Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific Principals, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the Principals in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

vi. Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

vii. Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

viii. Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

ix. Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

x. Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

xi. Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the Principals of this Declaration should not be accepted for publication.

xii. Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.