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PROTOCOL TITLE: Intraoperative Use of Intravenous Indocyanine Green (ICG) to Assess Ovarian Perfusion Using Infrared Imaging: A Feasibility Pilot Study

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	Indocyanine green (ICG)
IND / IDE / HDE #	
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees X N/A
Sample Size	30
Funding Source	Karl Storz
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study)

	☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☐ Yes ☐ No

1.0 OBJECTIVES:
To assess the feasibility of using intravenous ICG to characterize the vascular perfusion of ovaries during gynecologic surgery.

2.0 BACKGROUND:
2.1 Chemistry
Modern surgical techniques have incorporated the use functional imaging to better identify and target areas of interest. Indocyanine green (ICG) is a Food and Drug (FDA)-approved tricarbocyanine dye that is fluorescent under near-infrared (NIR) light. Excitation of ICG occurs between 750 and 800 nm. Its chemical formula is $C4_3H_{47}N_2NaO_6S_2$ (Han, Kankala, Wang, & Chen, 2018). ICG solutions for injection often contain sodium iodide. ICG is water soluble and when introduced intravenously, it is bound by plasma proteins, namely albumin. The intravascular half-life of ICG is 3-4 minutes with rapid hepatic clearance (Cherrick, Stein, Leevy, & Davidson, 1960). Clearance of ICG follows first-order kinetics and is eliminated exponentially in the first 10-20 minutes after administration. Trace amounts of ICG can remain in the system for more than an hour. ICG has no known metabolites .(Alander et al., 2012) The LD_{50} (lethal dose) of ICG is 50 – 80 mg/kg which is significantly greater than standard doses of less than 2 mg/kg (KARL STORZ Endoscopy - America, 2016). Rapid clearance of the dye allows it to be given over multiple injections, as needed, during a single procedure. After intravenous injection ICG is visible in organs within 1-2 minutes and remains visible for 20-120 minutes depending upon the organ of interest (KARL STORZ Endoscopy - America, 2016).

2.2 Clinical uses
Since the 1950s, ICG has been approved in the United States for intravenous administration. Early uses for ICG included measurement of hepatic function, cardiac output and retinal angiography (Rahimtoola & Swan, 1965; Yannuzzi, 2011). Today, ICG has been applied across several surgical specialties to improve intraoperative assessment and to reduce unnecessary tissue trauma. These uses are off-label but are a part of a growing body of literature that suggests ICG can be useful in assessments of tissue and organ perfusion. Selective sentinel lymph node resection is based on the observation that dye injected into tumor or tumor-adjacent tissues is taken up into the lymphatic system. The first lymph nodes to undergo dye uptake are known as sentinel lymph nodes and are representative of other lymph nodes within the same lymphatic chain. A dye negative SLN is proxy for a tumor free lymph node, making radical lymphadenectomy unnecessary and reducing complications from such dissections. This SLN concept has been employed in surgical oncology for many disciplines including breast, cervical and endometrial cancer.

Another major surgical application is intraoperative angiography to evaluate for preserved or recovered vascular perfusion (Arichi et al., 2014; Ferroni, Sentell, & Abaza, 2018). ICG fluorescence angiography has also been employed in colorectal surgery to identify anastomotic insufficiency, or poor perfusion of anastomoses after bowel resection. In PILLAR II, a prospective, multicenter clinical trial in colorectal surgery, fluorescence angiography using ICG was successful in 99% of cases and changed surgical plans in 8% (Jafari et al., 2015). In hepatobiliary surgery, ICG facilitates the identification of biliary anatomy and of tumor as it accumulates within the lesion (Baiocchi, Diana, & Boni, 2018). In plastic surgery, ICG has been

used to assess vascular anastomoses and tissue perfusion (de Vita & Buccheri, 2018). Neurosurgical uses of ICG have centered around the identification of vascular pathology (Reinhart, Huntington, Blair, Heniford, & Augenstein, 2016).

Gynecologic uses of ICG extend beyond tumor localization for cancer. Excisional endometriosis surgery may be technically challenging and the use of functional imaging can facilitate assessment of tissue perfusion after removal of lesions on the bowel or ovary (Bar-Shavit, Jaillet, Chauvet, Canis, & Bourdel, 2018). De Neef et all used ICG intraoperatively to identify rectovaginal deep infiltrating endometriosis (DIE) (De Neef et al., 2018). They reported a series of 6 patients undergoing laparoscopy for endometriosis in which 0.25 mg/kg ICG was injected intravenously at the time of skin incision. Rectovaginal DIE was then targeted using surgical NIR imaging equipment. Rectovaginal DIE, and superficial endometriotic lesions on the peritoneum were identified in every case. No intra- or postoperative complications were reported. The clinical utility of ICG during bowel resection for endometriosis has also been suggested, allowing real-time visualization of bowel perfusion and aid in the selection of location of bowel transection (Seracchioli, Raimondo, Arena, Zanello, & Mabrouk, 2018).

The purpose of this study is to determine the feasibility of intravenous ICG administration to facilitate assessments of ovarian vascular perfusion. Historically, assessment of ovarian perfusion has been performed visually or via ultrasound with Doppler evaluation. In a study of infertile patients, ovarian perfusion was assessed using transvaginal ultrasound with Doppler (Kupesic & Kurjak, 1997). A resistance index (RI) was calculated based on vascular flow with differential results based on phase of the menstrual cycle or presence of ovarian pathology. In patients with ovarian endometriomas, evidence of ovarian interstitial microvascular injury has been demonstrated similarly by the presence of low flow and high RI (Qiu et al., 2012). The use of ICG to evaluate ovarian perfusion specifically has not been reported. The use of ICG for intraoperative perfusion assessment of the ovary could provide more information about the health of the ovary and inform the surgical approach to ovarian pathology.

2.3 Formulation
Indocyanine green for injection can be prepared by reconstituting one 25 mg vial of ICG using one 10 mL of sterile water. This mixture contains 2.5 mg of dye per mL of solution. ICG must be used within 6 hours after reconstitution.

2.4 Adverse effects
The most common adverse reactions that have been reported include allergic reactions that range from urticarial (hives) to anaphylaxis. Because of the sodium iodide presence in ICG contraindications include patients with a history of allergy to iodides due to the risk of anaphylaxis (Storz).

2.5 Drug interactions
Listed drug interactions include preparations containing sodium bisulfite which reduce the absorption peak of ICG (KARL STORZ Endosscopy - America, 2016)

3.0 STUDY ENDPOINTS:
3.1 Primary Objectives:
3.1.1 To assess the feasibility of using intravenous ICG to characterize the vascular perfusion of ovaries.

3.1.2 To utilize infrared light to image and detect adnexal ICG uptake.

3.1.3 To qualitatively assess ovarian perfusion after ICG administration.

3.1.4 To quantitatively assess ovarian perfusion after ICG administration by analyzing the intensity of fluorescence on intraoperative imaging.

3.2 Secondary Objectives:
3.2.2 To qualitatively and quantitatively compare and contrast adnexal ICG uptake in the presence and absence of adnexal pathology.

4.0 STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):
ICG will be injected intravenously to assess ovarian perfusion in the presence or absence (control) of pathology. Near infrared fluorescence imaging will be used to illuminate the ICG. The extent of perfusion will be determined using digital imaging software.

ICG will be stored at the NM Investigational Pharmacy and administered intravenously by the anesthesiologist at the direction of the surgeon during surgical procedure.

5.0 PROCEDURES INVOLVED:
5.1.1 Patients who are scheduled to undergo surgery at Northwestern Memorial Hospital will be approached for recruitment of the study at their preoperative visit in the Center for Comprehensive Gynecology clinic. Research coordinator will review consent form with potential participant. Ample time will be left for participant questions and comprehension

5.2.1 The screening procedures include:
Informed consent: will be obtained for all potentially eligible participants. Once consented we will review subject eligibility referring to inclusion and exclusion criteria.

5.2.2 Medical History: Complete medical, surgical, gynecologic and obstetrical history, medications, allergies, social and family history.

5.2.3 Demographics
Age, gender, race, ethnicity, gravidity, parity.

5.2.4 Review previous and concomitant medications

5.2.5 Physical exam including vital signs (pulse and blood pressure), height and weight

5.3.1 Surgical Procedures Involved
Prior to injection, the ICG will be prepared under sterile conditions using a standard protocol for reconstitution that involves the following. One 25 mg vial of Indocyanine Green for Injection, USP will be reconstituted using one 10 mL Sterile Water for Injection, USP vial that is provided in the ICG for Injection Set. After reconstitution, each 25 mg vial of ICG contains 2.5 mg of dye per mL of solution. During surgery ICG will be administered intravenously via a peripheral or central line at the direction of the surgeon by the anesthesiologist. The injected amount will be a 3 mL solution of reconstituted ICG that contains a 7.5 mg dose of ICG. This will be followed by a 10 mL bolus of normal saline for injection per the manufacturer's recommendation. The total dose of dye injected should not exceed 2 mg/kg.
Visibility of the ICG fluorescence should occur within 1-2 minutes with a duration of 20-120 minutes (KARL STORZ Endosscopy - America, 2016)

5.3.2 Imaging and Near-Infrared Devices: Karl Storz will provide the light source, device D-Light P and the NIR CCU Module, H3-Link on the equipment handler in the operating room. Images will be taken with two NIR camera heads (H3-Z FI) and light cables

5.4.1 Data Analysis
Images will be stored on locked Northwestern Memorial computers which only the study team will be able to access. Once imaging data is complete, study team will collect basic intensity quantification utilizing both *ImageJ* and Photoshop software.

6.0 DATA AND SPECIMEN BANKING
No specimens will be collected or banked for future use.

7.0 STUDY TIMELINES
7.1 Participants will be consented and enrolled at their pre-operative appointment

7.2 Study duration includes the time during ICG administration, visualization and imaging. Because this will be performed intraoperatively during standard survey of the abdomen and pelvis no surgical delays will be incurred. No other procedures or visits are necessary for participants in this study. If a participant seeks further treatment in the future at the Center for Comprehensive Gynecology, study coordinator will approach previous participant and consent them to participate in the study again.

7.3 Once imaging data is complete, study team will collect basic intensity quantification using *ImageJ* or *Photoshop*

7.4 Image data will be analyzed as they become available

8.0 INCLUSION AND EXCLUSION CRITERIA
8.1 Inclusion Criteria
8.2.1 Patients attending a preoperative visit at the Center for Comprehensive Gynecology who will undergo surgery.

8.2 Exclusion Criteria
8.2.1 Not able to comprehend and sign a written consent

8.2.2 Patients with a history of allergy to iodides

8.2.3 Patients history of renal failure or uremia, and those on dialysis

9.0 PARTICIPANT POPULATION(S)
We plan to recruit, consent and enroll 30 participants. Prior studies in colorectal surgery that demonstrated the safety and feasibility of intraoperative use of ICG for assessment of tissue perfusion included over 100 patients. With this pilot study, we aim to lay the foundation for future studies of ovarian vascular perfusion using intravenous ICG.

10. RECRUITMENT METHODS
10.1 Patients who are scheduled to undergo surgery at Northwestern Memorial Hospital will be approached for recruitment in the study at their preoperative visit in the Center for Comprehensive Gynecology clinic.

10.2 Research coordinator will review consent form with potential participant leaving ample time for participants to review, comprehend and ask any questions about the consent form or the study. Consent will be reviewed in person when possible or reviewed in telehealth pre-op appointment using eConsenting process on REDCap.

11.0 WITHDRAWAL OF PARTICIPANTS
Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

11.1 Patient voluntarily withdraws from the study (follow-up permitted);

11.2 Patient withdraws consent (termination of treatment and follow-up);

11.3 Patient is unable to comply with protocol requirements;

11.4 Patient experiences toxicity that makes continuation in the protocol unsafe;

11.5 Treating physician will judge continuation on the study would not be in the patient's best interest;

11.6 Lost to follow-up. If a research subject decides against undergoing the surgical procedure and/or surgical case is cancelled, the subject may be considered lost to follow up.

12.0 RISKS TO PARTICIPANTS
12.1 All patients will be closely monitored by physician and nursing staff in the operating room and postoperative recovery area for the full duration of action of the ICG injection. ICG is considered a safe, well-studied medication.

12.2 Adverse Events
Rare adverse events include allergic reactions that range from urticarial (hives) to anaphylaxis. Because of the sodium iodide presence in ICG contraindications include patients with a history of allergy to iodides due to the risk of anaphylaxis (KARL STORZ Endoscopy – America, 2016). Because the patients will be under general anesthesia as is standard protocol for laparoscopy, the surgical and anesthesia teams will be able to easily manage any adverse reactions.

12.3 Drug interactions
Listed drug interactions include preparations containing sodium bisulfite which reduce the absorption peak of ICG (KARL STORZ Endoscopy - America, 2016)

Atropine; Hyoscyamine; Phenobarbital; Scopolamine: (Moderate) Phenobarbital may increase the clearance indocyanine green. The half-life of indocyanine green was lower in patients taking the drugs concomitantly compared to patients with normal and abnormal liver function taking no concomitant medications. The mechanism of interaction is unclear; those proposed in the medical literature include increased indocyanine green uptake by the liver cell, enhanced binding by specific hepatic carrier proteins, or more rapid excretion into bile.

Belladonna Alkaloids; Ergotamine; Phenobarbital: (Moderate) Phenobarbital may increase the clearance indocyanine green. The half-life of indocyanine green was lower in patients taking

the drugs concomitantly compared to patients with normal and abnormal liver function taking no concomitant medications. The mechanism of interaction is unclear; those proposed in the medical literature include increased indocyanine green uptake by the liver cell, enhanced binding by specific hepatic carrier proteins, or more rapid excretion into bile.

Haloperidol: (Moderate) Haloperidol may increase the clearance of indocyanine green. The half-life of indocyanine green was lower in patients taking the drugs concomitantly compared to patients with normal and abnormal liver function taking no concomitant medications. The mechanism of interaction is unclear; those proposed in the medical literature include increased indocyanine green uptake by the liver cell, enhanced binding by specific hepatic carrier proteins, or more rapid excretion into bile.

Heparin: (Moderate) Heparin products that contain sodium bisulfite may reduce the absorption peak of indocyanine green. Collection of blood samples for analysis should be performed with anticoagulants that do not contain sodium bisulfite.

Hydrochlorothiazide, HCTZ; Propranolol: (Minor) In a study of 9 healthy adults given 0.5 mg/kg of indocyanine green, propranolol decreased clearance by 21%.

Nifedipine: (Moderate) In a study of 9 healthy adults given 0.5 mg/kg of indocyanine green, nifedipine increased indocyanine green clearance by 14%.

Nitrofurantoin: (Moderate) Nitrofurantoin may increase the clearance of indocyanine green. The half-life of indocyanine green was lower in patients taking the drugs concomitantly compared to patients with normal and abnormal liver function taking no concomitant medications. The mechanism of interaction is unclear; those proposed in the medical literature include increased indocyanine green uptake by the liver cell, enhanced binding by specific hepatic carrier proteins, or more rapid excretion into bile.

Phenobarbital: (Moderate) Phenobarbital may increase the clearance indocyanine green. The half-life of indocyanine green was lower in patients taking the drugs concomitantly compared to patients with normal and abnormal liver function taking no concomitant medications. The mechanism of interaction is unclear; those proposed in the medical literature include increased indocyanine green uptake by the liver cell, enhanced binding by specific hepatic carrier proteins, or more rapid excretion into bile.

Primidone: (Moderate) Primidone may increase the clearance indocyanine green. The half-life of indocyanine green was lower in patients taking the drugs concomitantly compared to patients with normal and abnormal liver function taking no concomitant medications. The mechanism of interaction is unclear; those proposed in the medical literature include increased indocyanine green uptake by the liver cell, enhanced binding by specific hepatic carrier proteins, or more rapid excretion into bile.

Propranolol: (Minor) In a study of 9 healthy adults given 0.5 mg/kg of indocyanine green, propranolol decreased clearance by 21%.

13.0 POTENTIAL BENEFITS TO PARTICIPANTS

No direct benefit

14.0 DATA MANAGEMENT AND CONFIDENTIALITY

14.1 All collected date will be stored on a locked and secured Northwestern Memorial computer located in the Center for Comprehensive Gynecology. Only study team will have access to the data. Photos will be taken in the OR. Images will be collected after surgery and de-identified then uploaded into ImageJ and Photoshop for analysis. Only study team will conduct data analysis.

14.2 **Statistical procedures**: Images pixilation intensity will be assessed in ImageJ and Photoshop. A paired t-test will be used to assess a patient's ovary with pathology and the ovary without pathology two determine whether there are any differences in ICG intensity.

15.0 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

All patients will be closely monitored by physician and nursing staff in the operating room and postoperative recovery area for the full duration of action of the active medication. ICG is considered a safe, well-studied medication.

16.0 PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

All participants will have ample time to discuss any questions, concerns or comments about the study. Participants may also contact study coordinator after pre-operative visit if any other questions arise. Participant images will be de-identified and screening data will be secured on a locked Northwestern Memorial computer.

17.0 ECONOMIC BURDEN TO PARTICIPANTS

Participants who elect to participate in this study, may participate with no additional charges.

18.0 QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

The Center for Comprehensive Gynecology sees a number of pre-operative patients presenting for gynecologic surgery. Both PI and Co-PI have extensive research and surgical experience. Entire study team is CITI Biomedical Research Trained. Study team collaborated on the study protocol and each member is well versed in the study procedures and their study duties.