Clinical Study Protocol

PROTOCOL NUMBER
PP PLR 03

TITLE
A Randomized, Controlled, Parallel, Multicenter Study Assessing Perfusion Outcomes with PINPOINT® Near Infrared Fluorescence Imaging in Low Anterior Resection.

SHORT TITLE
PILLAR III

PROTOCOL VERSION
April 15, 2016

SPONSOR
Novadaq Technologies Inc.
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Mississauga, Ontario,
Canada, L4W 4T9

Confidential

PROTOCOL APPROVAL

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Version: April 15, 2016

Prepared by:

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29 Apr 2016
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PROTOCOL SUMMARY

Study Number and Title:

PP PLR 03: A Randomized, Controlled, Parallel, Multicenter Study Assessing Perfusion Outcomes with PINPOINT® Near Infrared Fluorescence Imaging in Low Anterior Resection (PILLAR III).

Clinical Phase: Pivotal Study/Non Significant Risk Medical Device

Study Objectives:

Primary:

- To demonstrate an improvement in post-operative anastomotic leak rate in low anterior resection procedures where colon and rectal tissue perfusion is evaluated using PINPOINT® endoscopic fluorescence imaging or SPY Elite® Intraoperative Imaging as an adjunct to standard surgical practice compared to surgical procedures performed according to standard surgical practice alone.

Secondary:

- To evaluate the ability of the PINPOINT system or SPY Elite system to provide sufficient visualization for assessment of blood flow and related tissue perfusion during the procedure.
- To evaluate the effectiveness of assessing perfusion of colon and rectal tissue using PINPOINT or SPY Elite in reducing the rate of post-operative abscess requiring surgical management.

Study Design

This is a randomized, controlled, parallel, multicenter study to determine the reduction in post-operative anastomotic leak rate in low anterior resection (LAR) procedures where colon and rectal tissue perfusion is evaluated using PINPOINT or SPY Elite as an adjunct to standard surgical practice compared to surgical procedures performed according to standard surgical practice alone. The study is a two-stage adaptive design that allows a mid-trial reassessment of sample size. Therefore, a minimum of 450 and a maximum of 1000 subjects will be enrolled at up to 40 centers in North America. Prior to enrolling study subjects, participating surgeons at each center will be trained to perform perfusion assessment with PINPOINT.

Screening:
Patients scheduled for an open, or minimally invasive low anterior resection for a rectal or rectosigmoid neoplasm with curative intent with a planned anastomosis located 10 cm or less from the anal verge will be evaluated at baseline to determine if they meet the inclusion/exclusion criteria of the protocol. Subjects will be assessed to determine overall health status, including demographics, vital signs and predictive factors that may influence surgical outcomes. Eligible patients who provide informed consent will be considered for inclusion into the study.

Day 0:
During anesthesia, subjects will be randomized (1:1) to either the PERFUSION (PFN) Arm or the STANDARD (STD) Arm. Subjects in each arm will be randomized according to an independently generated randomization scheme to receive either perfusion assessment with PINPOINT and/or SPY Elite during the surgical procedure or to receive the standard of care procedure. Randomization will be stratified by site and by whether or not the patient received prior neoadjuvant therapy.

Subjects in the PFN Arm will undergo a LAR according to the surgeon's standard practice with the addition of intraoperative imaging using PINPOINT and/or SPY Elite NIR fluorescence imaging to assess colon and rectal tissue perfusion during the following steps of the procedure:

- perfusion of proximal transection margin after IMA ligation; prior to bowel transection
- perfusion of the mucosal aspect of the completed anastomosis (with the exception of hand sewn coloanal anastomoses which will involve assessment of the mucosal aspect of the proximal colon only)

Subjects in the PFN Arm may also undergo additional or repeat intraoperative imaging using PINPOINT and/or SPY Elite NIR fluorescence imaging based on the surgeon's clinical judgment.

Subjects in the STD Arm will undergo a LAR according to the surgeon's standard practice only.

All subjects will receive the hospital/institution and surgeon's standard pre-operative, post-operative and post discharge care with the addition of any study specific requirements. An air leak test on all anastomoses (with the exception of hand sewn coloanal anastomosis when applicable) will be performed in the surgeon's standard fashion.

Details of the actual surgical technique will be documented post-operatively. The surgeon's ability to sufficiently assess blood flow and related tissue perfusion using PINPOINT or SPY Elite will be recorded. The final height of the anastomosis from the anal verge will be determined by assessing the markings on the stapler or by rigid proctoscopy, at the discretion of the surgeon. The site of the proximal anastomosis segment and the level of the inferior mesenteric artery and vein ligation will also be recorded.

Follow-up and Post-operative Complications:
All subjects will be followed to monitor occurrence of post-operative complications up to Week 8 post-surgery (±14d). All subjects will have study specific follow-up visits on Day 1, date of discharge, Week 8 and the date of ileostomy closure (if applicable). Subjects with a discharge date later than Week 8 who did not have an ileostomy, will be followed until the Week 8 visit. All subjects with a diverting ileostomy must have flexible sigmoidoscopy or proctoscopy and/or contrast enema to evaluate the anastomosis between 3 weeks postoperatively and the Week 8 visit (±14d).

Subjects who present with a clinical suspicion of anastomotic leak during the study who do not require urgent reoperation will have a CT scan with PO and, if diverted or if necessary, rectal contrast to confirm. A leak is considered confirmed if any evidence of endoluminal contents (air, fluid, GI contents or contrast material) through the anastomosis is identified by imaging, drain output or at reoperation, or by endoscopic evidence of an anastomotic defect. All scans will be reviewed by an independent radiologist for confirmation. The presence of infection or abscess thought to be related to the anastomosis may be classified as an anastomotic leak at the surgeon's discretion even if it cannot be definitively identified as visualized during an operation or by contrast extravasation. All anastomotic leaks will be followed until resolution.

All adverse events and post-operative complications occurring during the study period will be reported and graded according to the Clavien-Dindo system (Table 2).

Analysis of anastomotic leak rate will be based on the occurrence of a leak according to the protocol definition at any time during the study up to Week 8 (±14d).

Study Population:

The study will enroll a minimum of 450 and maximum of 1000 subjects scheduled to undergo an open or minimally invasive LAR. To be eligible for the study, subjects must meet the following main inclusion criteria:

- 18 years of age and older.
- Undergoing open, or minimally invasive LAR for the treatment of rectal or rectosigmoid neoplasms.
    - Subjects with rectal or rectosigmoid neoplasm(s) may be treated with or without neoadjuvant therapy. Long-course neoadjuvant therapy must have been completed ≥6 weeks prior to LAR surgery (Day 0).
- Have a planned low circular stapled or transanally hand sewn anastomosis ≤10 cm from the anal verge, with or without reservoir/pouch.

Subjects meeting any of the following criteria will be *excluded* from the study:

- Undergoing stapled anastomosis with the use of an experimental or non-FDA approved stapler.
- Undergoing ileoanal reconstruction, proctocolectomy, abdominoperineal resection, Hartmann's procedure, Hartmann's reversal or multiple synchronous colon resections (e.g., LAR and concomitant right colectomy).
- Subject has received and completed a course of pelvic radiotherapy ≥ 6 months prior to LAR surgery (Day 0).
- Subject has previously undergone a leftsided colon resection.
- Subject has previously undergone a rectal resection.
- Subject has recurrent rectal or rectosigmoid cancer.
- Has a diagnosis of locally advanced rectal or rectosigmoid cancer undergoing extended en bloc operations.
- Has a diagnosis of Stage IV rectal or rectosigmoid cancer with any multifocal metastases or single site metastasis with tumor size of > 2 cm.
  a. Intra operative incidental finding or preoperative suspicion of Stage IV cancer with isolated (single site) metastasis (≤ 2 cm) or limited metastases (≤3), with largest lesion ≤ 2 cm in size, does not exclude the subject.
- Diagnosis of inflammatory bowel disease.Hepatic dysfunction defined as MELD Score >12.
- Renal dysfunction with serum creatinine ≥ 2.0 mg/dL.
- Known allergy or history of adverse reaction to ICG, iodine or iodine dyes.
- Pregnant or lactating female.

Study Devices:

PINPOINT® Endoscopic Fluorescence Imaging System

An endoscopic fluorescence imaging system for high definition (HD) visible (VIS) light and near infrared (NIR) fluorescence imaging that includes the following components:

- A surgical endoscope optimized for VIS/NIR illumination and imaging.
- A camera head that is also optimized for VIS/NIR imaging and mounts to the endoscope eyepiece
- A flexible light guide cable.
- An endoscopic Video Processor/Illuminator for VIS/NIR illumination to the surgical endoscope via a flexible light guide cable, and the image processing required to generate simultaneous, real-time HD video color and NIR fluorescence images.
- A high-definition medical video recorder that allows the capture of still images and video.
- The PINPOINT PAQ containing the imaging agent and aqueous solvent.

SPY ELITE® Intraoperative Perfusion Assessment System.

An open intraoperative fluorescence imaging system for HD and NIR fluorescence imaging that includes the following components:

- SPY Elite® Device
- SPY Elite® PAQ containing the imaging agent, aqueous solvent and sterile drape.

The imaging agent used is indocyanine green (ICG), which is a sterile, water-soluble tricarbocyanine dye with a peak spectral absorption at 800-810 nm in blood plasma or blood. ICG contains not more than

5.0% sodium iodide.
Study Variables: **Primary:** Incidence of post-operative anastomotic leak in each study arm. **Secondary:** • Proportion of PERFUSION arm subjects in whom the PINPOINT or SPY Elite system provided sufficient visualization for assessment of blood flow and related tissue perfusion during the procedure. • Incidence of post-operative abscess in each study arm. Safety: • Incidence of treatment related adverse device events and surgical complications. • Clavien-Dindo grading of post-operative complications. • Concomitant medications and procedures.
Study Procedures and Assessments: The following tests and procedures will be performed: • Assessment of eligibility criteria. • Demographics, vital signs, height, weight, surgical predictive factors. • Hemoglobin measurement (pre-operative and Day 1). • Randomization to the PERFUSION or STANDARD Arm. • Low anterior resection according to surgeon's standard practice inclusive of the hospital/institution's standard pre-operative, post-operative and post discharge care. o Circular stapled or transanally hand sewn anastomosis. o Open or minimally invasive low anterior resection o Minimally invasive low anterior resection with or without hand-assist. o Minimally invasive low anterior resection with or without open-assist. o Conversion to open procedure. o Colorectal or coloanal reconstruction with or without reservoir/pouch. o Proximal diverting ileostomy as indicated. • PERFUSION Arm (only): o Imaging agent administration via central/peripheral IV line. o Perfusion assessments of colon transection margin prior to proximal transection. o Perfusion assessment of the proximal and distal mucosal aspect of completed anastomosis (except hand sewn coloanal anastomosis). • Assessment of adverse device effects up to 24 hrs. post-surgery. • Documentation of actual surgical technique. • Assessment of anastomotic leak, adverse events and other post-operative complications. o CT scan if clinical suspicion of anastomotic leak. • Classification of adverse events and post-operative complications using Clavien-Dindo system (Table 2). • Ileostomy closure. o Routine endoscopy and/or contrast enema of anastomosis between 3 weeks post-surgery and Week 8 visit if subject has an ileostomy. • Concomitant medications. • Follow-up visits on Day 1, date of discharge, Week 8, and date of ileostomy closure (if applicable). Subjects with a discharge date later than Week 8, who do not have an ileostomy, will have the last study visit at Week 8 visit. The last study visit for subjects with an ileostomy will occur on the date of closure, or at Week 8, whichever is earlier. Surgeon Qualification: • Training on use of PINPOINT by qualified Novadaq representatives. • Perform at least 3 perfusion assessment (proximal and transanal perfusion assessments) procedures with PINPOINT prior to enrolling subjects in the study. • Training on use of SPY Elite by qualified Novadaq representatives.

- Perform at least 3 perfusion assessment procedures (proximal only) with SPY Elite prior to using SPY Elite in the study.

Sample Size and Statistical Analysis:

The PILLAR III study is designed to allow a single mid-trial reassessment of sample size, employing the method of Mehta and Pocock[22]. A minimum of 450 and a maximum of 1000 subjects will be enrolled at up to 30 centers.. The trial will utilize a group sequential design with Pocock stopping boundaries with a planned sample size of 800 subjects. A futility boundary will also be incorporated. A single interim analysis will be conducted on the first 450 subjects enrolled with assessment of the primary endpoint. If the stopping boundary for trial success is not met at this interim analysis point and futility is not declared, the Mehta and Pocock method of sample size re-estimation based on promising zones will be applied to evaluate whether an increase in sample size above the planned 800 subjects is warranted (up to a maximum of 1.25 times the original planned sample size, i.e. 1000 subjects).

At the time of the interim analysis, the primary objective null hypothesis will be tested against the one-sided alternative hypothesis that the anastomotic leak rate in the PERFUSION arm is less than that experienced with the STANDARD surgical approach. If the p-value is less than a pre-specified threshold based on the Pocock stopping boundary, the null hypothesis will be rejected, whereas if the p-value is greater than the futility threshold, the trial will be considered futile. In either of these eventualities, no new enrollments will occur, and follow-up will only continue per regulatory requirements. However, if the p-value falls between these two thresholds, an evaluation of conditional power will be made to determine if a re-estimated larger sample size is warranted. The trial will then continue to either the planned sample size of 800 subjects or the re-estimated sample size of up to a maximum of 1000 subjects.

A modified Intent-to-Treat (mITT) analysis population will be utilized for the primary analysis. The first two specified secondary objectives are intended to support product labeling. They will be tested in sequential fashion. i.e., if and only if the primary objective passes according to the criteria above, testing will proceed to the first secondary objective (proportion of PERFUSION arm subjects in whom the PINPOINT or SPY Elite system provided sufficient visualization for assessment of blood flow and related tissue perfusion during the procedure). If and only if that objective passes, testing will proceed to the second secondary objective (incidence of abscess requiring surgical management). The standard for "passing" the secondary objectives will be a p-value less than 0.025 one-sided.

Study Duration:

The study is expected to begin in the first half of 2015 and complete enrollment within 24 months. Therefore, the study is expected to complete in 2017.

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ABBREVIATIONS AND DEFINITIONS

ADE	Adverse device effect
AE	Adverse event
AR	Anterior Resection
ASA	American Society of Anesthesiologists
AT	As-Treated
BMI	Body Mass Index
CFR	Code of Federal Regulations
CRF	Case Report Form
CT	Computerized Tomography
DSMC	Data and Safety Monitoring Committee
DRSI	Disposable Rigid Scope Introducer
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HD	High Definition
IA	Imaging Agent
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonization
ICG	Indocyanine Green
IMA	Inferior Mesenteric Artery
IMV	Inferior Mesenteric Vein
IPAA	Ileal Pouch – Anal Anastomosis
IR	Independent Radiologist
IRB	Institutional Review Board
IV	Intravenous
LAR	Low Anterior Resection
MELD	Model for End-Stage Liver Disease
mITT	Modified Intent-to-Treat
NGT	Nasogastric Tube
NIR	Near-Infrared
NPO	Nil per Os
PFN	Perfusion
PILLAR II	Perfusion Assessment in Laparoscopic Left Anterior Resection Multicenter study
PINPOINT	PINPOINT Endoscopic Fluorescence Imaging System
PO	Per Os
POD	Post-operative Day
PP	Per-Protocol
PSG	PILLAR III Study Group
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STD	Standard
US	United States
UADE	Unanticipated Adverse Device Effect
VIS	Visible

1 INTRODUCTION AND BACKGROUND

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and in compliance with the protocol, Good Clinical Practice (GCP) and all applicable regulations.

1.1 Background

This study will investigate the effectiveness of assessing perfusion of colon and rectal tissue using PINPOINT endoscopic fluorescence imaging (PINPOINT) or SPY Elite intraoperative imaging in reducing the post-operative anastomotic leak rate in low anterior resection (LAR).

LAR with low colorectal or low coloanal anastomosis is an accepted surgical technique for surgically treating rectal and rectosigmoid neoplasms. The American Society of Colon and Rectal Surgeons defines LAR as a colorectal resection with anastomosis of the colon to the extraperitoneal rectum[1] and defines an LAR with a coloanal anastomosis as a colorectal resection with anastomosis of colon to the anal canal circumferentially[1]. LAR may be accomplished by utilizing modern minimally invasive surgery techniques or by open surgery via laparotomy.

Minimally invasive techniques for LAR include conventional laparoscopic or laparoscopic hand-assisted procedures, and robotic surgery (da Vinci Surgery, Intuitive Surgical Inc.) or robotic-assisted laparoscopic procedures. Minimally invasive techniques for colorectal surgery have become more accepted in recent years due to patient related benefits that include reduced post-operative pain, earlier return of bowl function, shorter hospital stay and earlier ability to return to normal daily activities[2-4]. Laparoscopic surgery has also been shown to have lower post-operative complication and mortality rates as well as lower hospital costs[4].

Both minimally invasive and open methods are routinely performed. The decision to perform a minimally invasive or open procedure is made based on surgeon preference and training, surgical feasibility and patient anatomy and condition. Specifically, the tumor size and location, patient internal anatomy, obesity, and the effects of prior radiation will affect the ability of the surgeon to perform adequate resection in a minimally invasive fashion. These factors are considered when deciding to perform an open surgery versus a minimally invasive operation. Additionally, findings during a planned minimally invasive operation or a change in the patient's operative condition may cause the surgeon to convert to an open procedure during the operation. Converted surgery can be expected in 6-24% of cases[4].

Minimally invasive and open LAR procedures are both considered to be oncologically safe for the patient. Data indicates that the oncologic outcomes between minimally invasive and open resections for treatment of primary rectal cancer are the same[3]. A recent retrospective comparative study has shown that there is no significant difference in the 5 year local recurrence rate and cancer free survival rate between laparoscopic and open surgery[2].

There are a number of complications that can occur after LAR, with anastomotic complications being the most serious. Anastomotic bleeding, leaks, strictures, and fistulas are complications that may be related to surgical technical factors such as tension, stapler malfunction and tissue ischemia; or to patient related factors such as male sex, local sepsis, poor nutrition, immunosuppression, morbid obesity and/or radiation exposure[5]. Anastomotic leak is considered the most dreaded of complications and is reported to occur 3-20% of the time in colorectal surgery[6-10] and the risk increases for lower anastomoses. Anastomoses below 10 centimeters

(cm) from the anal verge have been shown to be a specific predictor of leak in a prospective study[7]. Another recent prospective randomized study in patients undergoing a colorectal resection (LAR, proctocolectomy, or Hartmann's reversal, with low colorectal or coloanal anastomosis or ileoanal pouch anal anastomosis [IPAA] procedures) with planned anastomosis ≤10 cm from the anal verge demonstrated an overall leak rate of 12%[11].

Anastomotic leaks can be devastating for the patient as they can cause significant morbidity and increased mortality. Surgical risks are minimized as much as possible by using proper technique in constructing the anastomosis and by temporary ileostomy when felt to be necessary. One of the key technical issues in mitigating risk of anastomotic leak is ensuring adequate tissue perfusion in the region of the anastomosis. The blood supply of the distal and/or proximal segments of colon are thought to affect anastomotic healing and blood flow reduction at the rectal stump has been shown to be associated with an increased rate of anastomotic leak[12]. Standard surgical care includes an assessment which can include visualization by white light, palpation of the mesentery, bleeding from the cut edge when the colon or rectum is divided and visible blood flow from the cut marginal artery when dividing the colon and mesentery for the proximal margin of resection. These techniques are used variably by surgeons with no true objective measure to guide treatment. Intraoperative near infrared (NIR) fluorescence imaging to assess colon and rectal tissue perfusion is a relatively new technique that may help to reduce the risk of leaks occurring as a result of inadequate perfusion. Several studies published within the last 4-5 years have shown results that suggest NIR fluorescence imaging may play a role in reducing anastomotic leaks.

PINPOINT acquires near-infrared (NIR) fluorescence images of an imaging agent (indocyanine green [ICG]) to allow for visual assessment of colon and rectal tissue perfusion during surgery. The recently completed PILLAR II Multicenter Study (PILLAR II) investigated the utility and feasibility of intra-operative perfusion assessment using PINPOINT in LAR procedures with a planned anastomosis 5-15 cm from the anal verge. Results indicate that PINPOINT is a safe and feasible tool for intra-operative assessment of tissue perfusion during colorectal resection and may lead to a decreased incidence of anastomotic leak[13].

1.2 Previous Human Experience

Several studies using similar technology to PINPOINT and SPY Elite have been conducted to investigate the feasibility of using NIR ICG induced fluorescence angiography in assessing tissue perfusion during colorectal resection to potentially reduce the rate of anastomotic leak have been published.

The PILLAR II study was conducted to demonstrate the utility and feasibility of intra-operative perfusion assessment using PINPOINT NIR ICG induced fluorescence angiography at the time of anastomosis creation[13].

One hundred and forty-seven patients were enrolled, of whom 139 were eligible for final analysis. The average age of patients was 58 ±14 years, and 53% of patients were male. Obesity (Body Mass Index [BMI] >30) was prevalent in 30% and the majority of patients were American Society of Anesthesiologists (ASA) II (53%). Diverticulitis (44%), rectal cancer (25%) and colon cancer (21%) were the most prevalent pre-operative diagnoses. Of the patients with rectal cancer (N=35), 43% underwent pre-operative pelvic radiation. Cardiovascular disease (44%), and urogenital disease (40%) were the most prevalent comorbidities.

Laparoscopic resection was attempted in 86% and robotic surgery in 14% of the patients imaged. There was an overall conversion rate of 7.8% (N=12), of which 5 patients were imaged, and 7 patients were dropped out of analysis due to intraoperative decision to not image. The splenic flexure was mobilized in 81% of patients, and a high ligation of the inferior mesenteric artery (IMA) was performed in 62% of cases. Successful imaging was obtained in 98.6% of cases in which perfusion imaging was attempted. Imaging was unsuccessful in 2 patients secondary to equipment malfunction. Fluorescence angiography imaging changed the surgical plan in 11 (7.9%) patients. This included revision of the point of proximal colon transection as indicated by perfusion assessment in 9 patients (6.5%); takedown and revision of anastomosis after transanal perfusion assessment in one patient; and confirmation of viability of anastomosis where there was concern based on white light imaging in one patient. The use of fluorescence angiography with findings of adequate perfusion altered the intraoperative plan for diversion to no diversion in this patient. There were no anastomotic leaks in the 11 patients in whom a change in the surgical plan occurred based on fluorescence angiography findings.

Post-operative morbidity was reported in 17% of patients of which 12% was secondary to surgical procedure and 2 (1.4%) were severe in nature. There were only 2 (1.4%) anastomotic leaks reported, both diagnosed clinically and confirmed via radiological findings. Both patients had low ligation of IMA with an end-to-end anastomosis without diversion. One patient had rectal cancer with no history of pre-operative chemotherapy/radiation and underwent a laparoscopic low anterior resection with anastomosis at 6 cm, with splenic flexure mobilization, and had an operative time of 6 hours. A defect of the anastomosis on Computed Tomography (CT) scan obtained due to clinical suspicion on postoperative day 12 was discovered, and the patient was treated with a re-admission, antibiotics and transgluteal percutaneous drainage without diversion. The second patient had a diagnosis of diverticulitis, and underwent a laparoscopic anterior resection with anastomosis at 11cm and an operative time of 3 hours. Patient was diagnosed on post-operative day 12 by CT scan, which showed a small abscess containing air adjacent to the anastomosis and was treated with re-admission and antibiotics. Both patients had full resolution of symptoms and no further treatment was required.

1.3 Potential Risks and Benefits to Human Subjects

PINPOINT is classified by the United States Food and Drug Administration (FDA) as a Class II medical device with a Product Code of GCJ. PINPOINT is not identified as a significant risk device on the FDA Information Sheet titled "Significant Risk and Non-significant Risk Medical Device Studies". PINPOINT is a commercially available product in the United States (US). PINPOINT has a 510(k) clearance from the FDA for the following indication:

"The PINPOINT system is intended to provide real-time endoscopic visible and endoscopic NIR fluorescence imaging. PINPOINT enables surgeons to perform routine visible light endoscopic procedures as well as further visually assess vessels, blood flow and related tissue perfusion with near infrared imaging during minimally invasive surgery".

SPY Elite is classified by the United States FDA as a Class II medical device with a Product Code of IZI. SPY Elite is a commercially available product in the United States. SPY Elite has a 510(k) clearance from the FDA for the following indication:

"The SPY Elite System is an imaging system used in capturing and viewing fluorescence images for the visual assessment of blood as an adjunctive method for the evaluation of

tissue perfusion, and related tissue-transfer circulation in tissue and free flaps used in plastic, micro, reconstructive, gastrointestinal, and cardiovascular surgical procedures"

The imaging agent, ICG is approved for human use by the FDA. The most serious risk of ICG when administered intravenously in humans, is anaphylactic death, which has been reported following ICG administration during cardiac catheterization[14,15].

These and other risks of the PINPOINT system or SPY Elite system in humans are described further in Section 7, Risks/Precautions. For more detailed information, please refer to the PINPOINT Operator's Manual[16] or SPY Elite Operator's Manual[18].

2 STUDY OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

To demonstrate an improvement in post-operative anastomotic leak rate in low anterior resection procedures where colon and rectal tissue perfusion is evaluated using PINPOINT Endoscopic Fluorescence imaging or SPY Elite Intraoperative imaging as an adjunct to standard surgical practice compared to surgical procedures performed according to standard surgical practice alone.

2.1.2 Secondary Objectives

To evaluate the ability of the PINPOINT system or SPY Elite system to provide sufficient visualization for assessment of blood flow and related tissue perfusion during the procedure.

To evaluate the effectiveness of assessing perfusion of colon and rectal tissue using PINPOINT or SPY Elite in reducing the rate of post-operative abscess requiring surgical management.

3 INVESTIGATIONAL PLAN

3.1 Study Design Overview

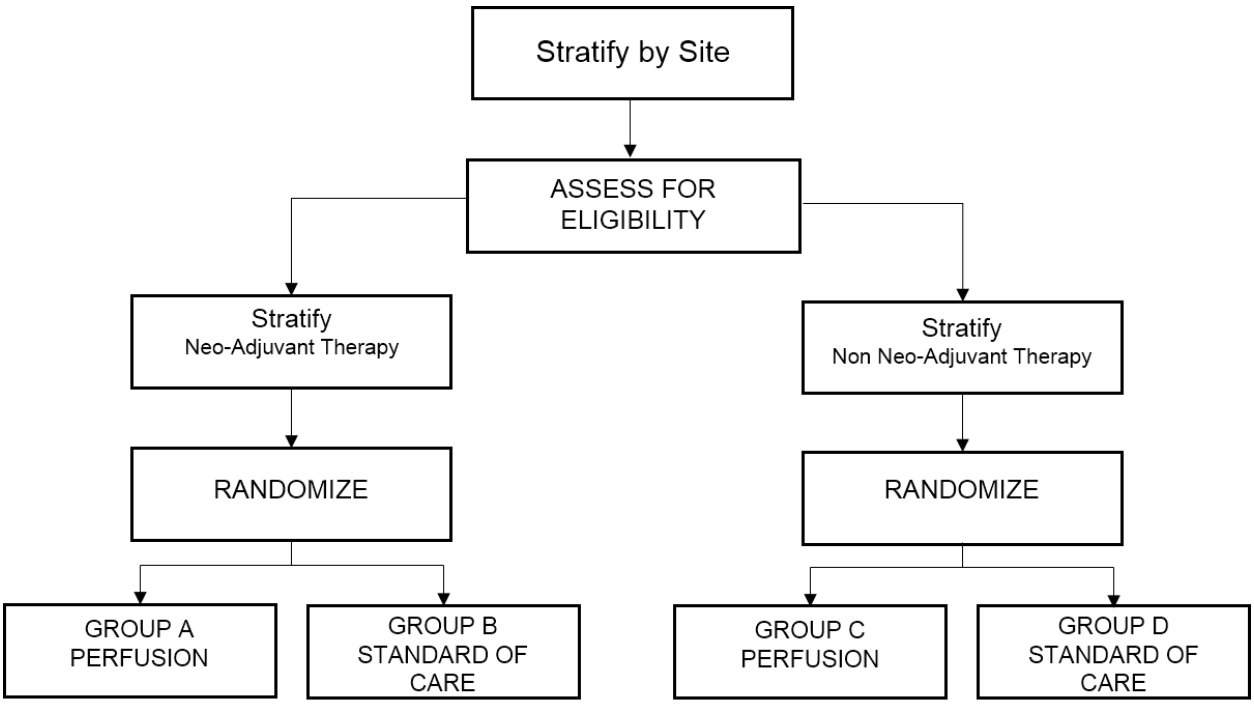
This is a randomized, controlled, parallel, multicenter study to determine the difference in post-operative anastomotic leak rate in low anterior resection procedures where colon and rectal tissue perfusion is evaluated using PINPOINT and/or SPY Elite as an adjunct to standard surgical practice compared to surgical procedures performed according to standard surgical practice alone. The study incorporates a two-stage group sequential adaptive design that allows a single interim look and a mid-trial reassessment of sample size. The planned sample size is 800 subjects with a minimum of 450 and a maximum of 1000 subjects to be enrolled at up to 40 centers in North America. Prior to enrolling study subjects, participating surgeons at each center will be trained to perform perfusion assessment with PINPOINT and SPY Elite.

Screening:
Patients scheduled for a minimally invasive, or open low anterior resection (LAR) with a planned anastomosis located 10 cm or less from the anal verge will be evaluated at baseline to determine if they meet the inclusion/exclusion criteria of the protocol. Subjects will be assessed to determine overall health status, including demographics, vital signs and predictive factors that may influence

surgical outcomes. Eligible patients who provide informed consent will be considered for inclusion into the study.

Day 0:
During anesthesia, subjects will be randomized (1:1) to either the PERFUSION (PFN) Arm or the STANDARD (STD) Arm. Subjects in each group will be randomized according to an independently generated randomization scheme to receive perfusion assessment with PINPOINT and/or SPY Elite during the surgical procedure or to receive the standard of care procedure. Randomization will be stratified based on investigative site and prior neoadjuvant therapy. Subjects are considered enrolled upon randomization.

FIGURE 1. Group Assignment and Randomization



Subjects in the PFN Arm will undergo a LAR according to the surgeon's standard practice with the addition of intraoperative imaging using PINPOINT and/or SPY Elite NIR fluorescence imaging to assess colon and rectal tissue perfusion during the following steps of the procedure:

- assessment of proximal transection margin of the colon after IMA ligation; prior to transection.
- assessment of the mucosal aspect of the completed anastomosis (with the exception of hand sewn coloanal anastomoses which will involve assessment of the mucosal aspect of the proximal colon only)

Subjects in the STD Arm will undergo a LAR according to the surgeon's standard practice only.

All subjects will receive the hospital/institution and surgeon's standard pre-operative, post-operative and post discharge care with the addition of any study specific requirements. An air leak test on all anastomoses (with the exception of hand sewn coloanal anastomosis when applicable) will be performed in the surgeon's standard fashion and documented.

The LAR procedure will adhere to the ASCRS Practice Parameters for the Management of Rectal Cancer[19] and will include mobilization and early devascularization (e.g. IMA and IMV ligation) as well as splenic flexure mobilization. Details of the actual surgical technique including use of hand-assisted technique and/or conversion to open, and any changes to the operative plan will be documented post-operatively. The surgeon's ability to sufficiently assess blood flow and related tissue perfusion using PINPOINT and/or SPY Elite will be recorded for subjects in the PFN Arm. The final height of the anastomosis from the anal verge will be determined by assessing the markings on the stapler or by rigid proctoscopy at the discretion of the surgeon. The site of the proximal anastomosis segment and the level of the inferior mesenteric artery and vein ligation will be recorded[17].

Follow-up and Post-operative Complications:
All subjects will be followed to monitor occurrence of adverse events (AE) and post-operative complications up to Week 8 (56 ±14 days) post-surgery. All subjects will have study specific follow-up visits on Day 1, date of discharge, Week 8 and the date of ileostomy closure (if applicable). Subjects with a discharge date later than Week 8, will be followed until discharge if the Investigator documents that the extended hospitalization is directly related to the surgical procedure or the PINPOINT and/or SPY Elite System. All subjects with a diverting ileostomy must have endoscopy and/or contrast enema of the anastomosis between 3 weeks post-surgery and the Week 8 visit (±14 days).

Subjects who present with a clinical suspicion of anastomotic leak during the study who do not clinically require an urgent reoperation will have a CT scan with PO and, if necessary, rectal contrast to confirm. A leak is considered confirmed if endoluminal contents (air, fluid, GI contents or contrast material) through the anastomosis is identified by imaging, drain output or at reoperation. The scans will be reviewed by an independent radiologist for confirmation. The presence of infection or abscess thought to be related to the anastomosis may be classified as an anastomotic leak at the surgeon's discretion even if it cannot be definitively identified as visualized during an operation or by contrast extravasation. All anastomotic leaks will be followed until resolution.

For patients with a diverting ileostomy, a leak may be identified by direct visualization of an anastomotic defect via sigmoidoscopy or by rectal contrast imaging, regardless of presence or absence of clinical symptoms.

All AE and post-operative complications occurring during the study period will be reported and graded according to the Clavien-Dindo system[20].

Analysis of anastomotic leak rate will be based on the occurrence of a leak according to the protocol definition at any time during the study up to Week 8.

This study is evaluating the utility of the PINPOINT or SPY Elite system only, and therefore the study protocol describes the requirements and use of these devices only.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Number of Subjects

A minimum of 450 and a maximum of 1000 subjects will be enrolled.

4.2 Inclusion Criteria

To be eligible for the study, a subject must fulfill all of the following criteria:

1. Be 18 years of age or older.
2. Be undergoing open, or minimally invasive LAR for the treatment of a rectal or rectosigmoid neoplasm.
    a. Subjects with rectal or rectosigmoid neoplasm(s) may be treated with or without neoadjuvant therapy. Long-course neoadjuvant therapy must have been completed ≥6 weeks prior to LAR surgery (Day 0).
3. Have a planned low circular stapled or transanally hand sewn anastomosis ≤10 cm from the anal verge.
4. Have a colorectal or coloanal reconstruction with or without reservoir/pouch.
5. Subjects who are women of child-bearing potential must not be pregnant or lactating, must have a negative pregnancy test at Day 0.
6. Have signed an approved informed consent form for the study.
7. Be willing to comply with the protocol.

4.3 Exclusion Criteria

A subject meeting any of the following criteria will be excluded from the study:

1. Undergoing stapled anastomosis with the use of an experimental or non-FDA approved stapler.
2. Undergoing ileoanal reconstruction, total colectomy or proctocolectomy, abdominoperineal resection, Hartmann's procedure, Hartmann's reversal or multiple synchronous colon resections (e.g., LAR and concomitant right colectomy).
3. Has received and completed a course of pelvic radiotherapy ≥ 6 months prior to LAR surgery (Day 0).
4. Has previously undergone a left sided colon resection.
5. Has previously undergone a rectal resection.
6. Has recurrent rectal or rectosigmoid cancer.
7. Has a diagnosis of locally advanced rectal or rectosigmoid cancer undergoing extended en bloc operations.
8. Has a diagnosis of Stage IV rectal or rectosigmoid cancer with any multifocal metastases or single site metastasis with tumor size of > 2 cm

    a. Intraoperative incidental finding or preoperative suspicion of Stage IV cancer with isolated (single site) metastasis (≤ 2 cm) or limited metastases (≤3), with largest lesion ≤ 2 cm in size, does not exclude the subject.

9. Has a diagnosis of inflammatory bowel disease (IBD). Subjects with rectal or rectosigmoid cancer neoplasms and IBD are excluded.

10. Has hepatic dysfunction defined as Model for End-Stage Liver Disease (MELD) Score >12.
11. Renal dysfunction defined as creatinine ≥ 2.0 mg/dL.
12. Has known allergy or history of adverse reaction to ICG, iodine or iodine dyes.
13. Has, in the Investigator's opinion, any medical condition that makes the subject a poor candidate for the investigational procedure, or interferes with the interpretation of study results.
14. Is actively participating in another investigational clinical study which, in the Investigator's or Sponsor's opinion, would interfere in this study.

4.4 Withdrawal of Subjects

Subjects can voluntarily withdraw (or be withdrawn) at any time during the study.

Investigators may withdraw a subject from the study because:

- A new health condition, diagnosis or finding appears that is suspected to require care or medication prohibited by the protocol.
    - e.g., the planned surgical procedure is modified to a procedure prohibited by the protocol.
- The subject has unacceptable adverse events.
- It is in the subject's best interest according to the Investigator's clinical judgment.

If a subject is prematurely withdrawn from the study, the reason(s) for withdrawal must be recorded on the subject's Subject Completion case report form (CRF).

Subjects who discontinue the study prematurely will not be replaced.

5 RANDOMIZATION, BLINDING AND SUBJECT IDENTIFICATION PROCEDURES

5.1 Randomization

Patients will be prospectively randomized into the PILLAR III Clinical Trial. Randomization will occur at the time of surgery, just after induction of anesthesia. Prior to surgery the patient will have provided written informed consent, completed all baseline procedures and met the requirements of the study inclusion and exclusion criteria. Randomization should be performed as closely as possible to the point of resection to minimize the incidence of dropout.

Patients will be randomly assigned on a one to one (1:1) basis to either the PERFUSION group (PFN) or the STANDARD group (STD). Randomization will be stratified by study site and within site by the patients history of prior neoadjuvant therapy (chemotherapy and/or radiation vs. non-neoadjuvant therapy) to ensure a more even distribution of baseline neoadjuvant therapy between treatment groups. Permuted block randomization will be performed within strata. To minimize the opportunity for the sequence to be predicted, the block size will be variable and randomly chosen from small multiples of 2 (i.e. 2, 4 or 6). The randomization schedules for all strata will be generated in advance by the contracted study statistician or designee using a computerized

random number generator. Investigational sites and the Study Sponsor will not have access to the randomization schedules.

Randomization will be accomplished using a sequential numbered sealed envelope system. Due to stratification for prior neoadjuvant therapy, a box of envelopes will be supplied for each strata (one for subjects who have received prior neoadjuvant therapy and another for subjects who have not received prior neoadjuvant therapy). Envelope seals are broken and treatment assignment is made only after verification of proper informed consent execution and study eligibility. In order to prevent any attempts to subvert the randomization process, the subject's initials, date of birth and date of randomization will be written on the randomization card. The randomization card will be signed by the study coordinator performing the randomization procedure and a second researcher who will witness the randomization procedure.

5.1.1 Randomization Procedure

The study coordinator or a designee will log into the EDC system and be asked a series of questions verifying that the patient is eligible and that informed consent has been obtained prior to initiating the randomization process. Once the subject is under anaesthesia, the study coordinator will select the randomization envelope with the lowest randomization number from the neoadjuvant or non-neoadjuvant randomization box depending on if the subject has received prior neoadjuvant therapy or not. The study coordinator will then disclose the randomization assignment to the Investigator. The study coordinator will then write the subject's initials, date of birth, and date of randomization on the randomization card. A second study coordinator or designee will witness the randomization procedure and will sign and date the randomization card verifying that the randomization procedure was followed correctly. The randomization card will be maintained in the subject's file. As there is no ability for a sham comparison, the investigator cannot be blinded to the use of the PINPOINT or SPY Elite device. Patients will be blinded to their randomization assignment until after the procedure.

A subject is not randomized until a randomization envelope seal has been broken. The randomization procedure should not be initiated unless the EDC system confirms that a patient is eligible and verifies baseline information. If any deviations occur (errors such as misplacing envelopes), or if the randomization assignment is made incorrectly, the clinical site will be required to contact the Sponsor and await guidance on how to proceed.

If, at any time after randomization, the subject becomes ineligible or withdraws, the subject is still considered randomized. If an intraoperative decision is made to perform a procedure other than what was intended, the subject will be categorized with respect to the definitions outlined for the analysis populations (see the Statistical Methods Section 10.6).

5.2 Subject Identification

Screening ID Number: All subjects screened for the study shall be assigned a 5-digit "screening" number on the Screening Log and if they are randomized, will subsequently be assigned a Subject Identification Number in the electronic data capture system. The Screening Identification Number shall be unique and categorize a subject in sequence of screening by an "S" followed by a 5-digit number. The first 2 digits identify the site and the last three digits identify the subject. For example, the first subject screened at site 01 is identified as screening number S-01-001. The screening log shall be maintained by the site to identify those subjects that have failed screening with the

reason why they did not qualify for enrollment. The screening number will be assigned sequentially within each study center in order of subject presentation for screening.

Enrolled Subject ID Number: Once a subject is randomized, they will be assigned a Subject Identification Number which is also a 5-digit number. The first two digits of the Subject Identification Number identify the site and the last three digits identify the subject. Each site will be given a Site Identification Number. For example, the first subject randomized at site 01 is identified as subject 01-001, the next subject as 01-002, etc.

6 STUDY TREATMENTS

6.1 PINPOINT Endoscopic Device Specifications

PINPOINT is an endoscopic fluorescence imaging system for high definition (HD) visible (VIS) light and near-infrared (NIR) fluorescence imaging. PINPOINT includes the following components:

- A surgical endoscope optimized for VIS/NIR illumination and imaging, which is available in different diameters, lengths and directions of view (Model: SC9100, SC9130).
- A camera head that is also optimized for VIS/NIR imaging and mounts to the endoscope eyepiece (Model: PC9002).
- A flexible light guide cable (Model: PC9004).
- An endoscopic Video Processor / Illuminator (VPI) capable of providing VIS/NIR illumination to the surgical endoscope via a flexible light guide cable, and the image processing required to generate simultaneous, real-time HD video color and NIR fluorescence images (Model: PC9001).

PINPOINT is designed to be connected to a medical-grade HD color monitor, such as those normally used in surgical endoscopy.

- PINPOINT Procedure Kits with Introducer containing the imaging agent, aqueous solvent and disposable rigid scope introducer (DRSI)[21].

PINPOINT is connected to a high-definition medical video recorder (Sony HVO-1000) that allows the capture of still images and video during operation.

PINPOINT acquires NIR fluorescence images of an imaging agent (ICG) to allow for visual assessment of vessels, blood flow and related tissue perfusion during minimally invasive, or open surgery. For the purpose of this study, PINPOINT will be used to assess perfusion of colon and rectal tissue during low anterior resection procedures.

PINPOINT Procedure Kits are supplied as part of the PINPOINT System. The PINPOINT PAQ® contains 6 procedure kits and is indicated for use exclusively with PINPOINT.

Each PINPOINT PAQ® (Product code: PP9036) contains:

- One box of sterile indocyanine green for injection, USP that contains:
  - Six single use 25 mg vials of ICG
  - Six single use 10 ml ampules of sterile Aqueous solvent

- Twelve 3 ml syringes, sterile
- Twelve 10 ml syringes, sterile
- Six 3-way stopcocks, sterile
- Twelve needles, 18G, 1 inch, sterile
- Labels for syringes

The PINPOINT Operator's Manual describes the contents, use and storage of the PINPOINT PAQ's. Instructions for preparation, handling and administration of ICG are also provided in the PINPOINT Operator's Manual.

PINPOINT allows simultaneous display of multiple images. Real time NIR fluorescence video images are acquired by using the imaging agent and may be viewed in two ways:

PINPOINT image: NIR fluorescence is superimposed in pseudo-color (green) on a white light image

SPY image: A black and white NIR fluorescence image is displayed

PINPOINT also operates as a conventional endoscopic imaging system and provides illumination for real-time color (white light) HD video imaging in the area of interest.

PINPOINT is a commercially available product in the United States (US). PINPOINT has a 510(k) clearance from the FDA for the following indication:

"The PINPOINT system is intended to provide real-time endoscopic visible and endoscopic NIR fluorescence imaging. PINPOINT enables surgeons to perform routine visible light endoscopic procedures as well as further visually assess vessels, blood flow and related tissue perfusion with near infrared imaging during minimally invasive surgery".

PINPOINT is manufactured by Novadaq Technologies Inc. (Novadaq). Please refer to the current version of the PINPOINT Operator's Manual[16] for a full description and specifications of the system.

6.2 SPY Elite Intraoperative Device Specifications

SPY Elite is an intraoperative fluorescence imaging system that allows surgeons to capture, review, print and archive high-quality fluorescence images of blood flow in vessels and micro-vessels, tissue and organ perfusion, in real-time during the course of performing a wide variety of surgical procedures.

The SPY Elite System consists of the following components:

- SPY Elite Device
- SPY Elite Kit

The SPY Elite device consists of the following components:

- An imaging head and camera system capable of capturing, archiving and replaying fluorescence images, an articulating arm and a mobile cart (LC3000)
- A touch screen monitor, glide-pad and keyboard

- SPY Elite Imaging System Software and SPY Elite analysis tool kit
- SPY Elite PAQs containing the imaging agent, aqueous solvent and sterile drapes

SPY Elite PAQs are supplied as part of the SPY Elite System. The SPY Elite PAQ® contains 6 procedure kits and is indicated for use exclusively with SPY Elite

Each SPY Elite procedure kit (Product code: LC3201) contains:
- One 25 mg vial of sterile indocyanine green for injection, USP
- One ampule Sterile Aqueous Solvent
- One SPY Elite Sterile Drape
- One SPY Elite Kit IFU

SPY Elite is an open-field NIR fluorescence system that utilizes the same mode of action as the PINPOINT System to allow for visual assessment of vessels, blood flow and related tissue perfusion during gastrointestinal procedures. For the purpose of this study, SPY Elite may only be used to assess perfusion of the colon prior to proximal transection during the low anterior resection procedures at the investigator's discretion.

SPY Elite allows for real time NIR fluorescence video images which are acquired by using the imaging agent and may be viewed in SPY image mode (A black and white NIR fluorescence image)

SPY Elite is classified by the United States FDA as a Class II medical device with a Product Code of IZI. SPY Elite is a commercially available product in the United States. SPY Elite has a 510(k) clearance from the FDA for the following indication:

"The SPY Elite System is an imaging system used in capturing and viewing fluorescence images for the visual assessment of blood as an adjunctive method for the evaluation of tissue perfusion, and related tissue-transfer circulation in tissue and free flaps used in plastic, micro, reconstructive, gastrointestinal, and cardiovascular surgical procedures".

SPY Elite is manufactured by Novadaq Technologies Inc. (Novadaq). Please refer to the current version of the SPY Elite Operator's Manual[19] for a full description and specifications of the system.

6.3 Imaging Agent Specifications

The imaging agent (IA), ICG (indocyanine green for injection, USP) 25 mg for Injection in the form of a sterile lyophilized powder containing indocyanine green with no more than 5% sodium iodide is approved by the FDA for determining cardiac output, hepatic function and liver blood flow, and for ophthalmic angiography via intravascular administration[14,15]. ICG is also approved under a 510(k) by the FDA for assessing blood flow and tissue perfusion in a variety of surgical and non-surgical procedures[16,18]. ICG can be administered intravenously or intra-arterially. It absorbs light in the near-infrared region at 806 nm, and emits fluorescence (light) at a slightly longer wavelength, 830 nm. When injected intravenously, ICG rapidly and extensively binds to plasma proteins and is confined to the intravascular compartment with minimal leakage into the interstitium. This property makes it an ideal agent for the acquisition of high quality images of the vasculature (i.e., for NIR fluorescence angiography).

The imaging agent is supplied as part of the PINPOINT PAQ or SPY Elite PAQ for distribution with PINPOINT or SPY Elite and is indicated for use exclusively with PINPOINT or SPY Elite.

6.3.1 Installation, Training and Storage

PINPOINT (and SPY Elite, if requested) will be installed by Novadaq representatives. The Investigator(s) and study staff shall be required to participate in training on the operational and procedural use of PINPOINT and SPY Elite as it relates to the conduct of this study. Training will be provided by Novadaq.

Prior to enrollment, participating Investigator surgeons must be experienced in the use of PINPOINT for assessing perfusion of colon and rectal tissue via participation in the PILLAR II study or via current ongoing use of a PINPOINT system installed at the study center.

Participating Investigators must also be experienced in the use of SPY Elite for assessing perfusion of colon and rectal tissue (proximal imaging only) via current ongoing use of a SPY Elite system at the study center, prior to utilizing SPY Elite in the study.

Investigator surgeons new to this technique will receive PINPOINT (and SPY Elite, if requested) training consisting of the following:

- Didactic training on product and procedure.
- Hands on training session with clinical educators on site.
- Guidance on use of PINPOINT and interpretation of the images with a clinical educator during a minimum of 3 cases prior to study enrollment.
- Guidance on use of SPY Elite and interpretation of the images with a clinical educator during a minimum of 3 cases prior to the use of SPY Elite in the study.

Supporting personnel operating and cleaning PINPOINT or SPY Elite will also receive training and be familiar with all applicable aspects of the operation and cleaning of the system.

PINPOINT and SPY Elite should be stored at room temperature in a secure and limited access area available to study staff.

6.4 Concomitant Treatment

Any concomitant medications the subject is receiving at the start of the study (Day 0) or given for any reason during the study must be recorded in the CRF and source documents with the exception of routine medications given for preparation of surgery, during surgery and post-operative care. These include but are not limited to the following:

- Sedatives and anesthetics
- Anticoagulants
- Prophylactic antibiotics
- Laxatives, diuretics and antacids
- Routine post-operative pain medications

The drug name, start and stop dates, indication, dose, frequency, and route information will be recorded for concomitant medications.

Other surgical and diagnostic procedures (e.g., endoscopy) concomitant to the LAR that take place during the study must be recorded in the CRF and in the source document, including start and stop dates.

7 RISKS/PRECAUTIONS

Refer to the PINPOINT Operator's Manual for a full description of the risks and precautions associated with all components of PINPOINT. The entire PINPOINT Operator's Manual should be read before using PINPOINT. Failure to follow the instructions and warnings in the manual may result in unsafe operation of the system and/or injury to the patient or operator.

Refer to the SPY Elite Operator's Manual for a full description of the risks and precautions associated with all components of SPY Elite. The entire SPY Elite Operator's Manual should be read before using SPY Elite. Failure to follow the instructions and warnings in the manual may result in unsafe operation of the system and/or injury to the patient or operator.

7.1 PINPOINT System – Endoscopes, Camera and Video Processor Illuminator Unit

PINPOINT is classified by the FDA as a Class II medical device with a Product Code of GCJ. PINPOINT is not identified as a significant risk device on the FDA Information Sheet titled "Significant Risk and Non-significant Risk Medical Device Studies".

PINPOINT should only be used according to its approved Indication for Use and according to the study procedures described in this protocol.

7.2 SPY Elite System.

SPY Elite is classified by the FDA as a Class II medical device with a Product Code of IZI. SPY Elite is not identified as a significant risk device on the FDA Information Sheet titled "Significant Risk and Non-significant Risk Medical Device Studies".

SPY Elite should only be used according to its approved Indication for Use and according to the study procedures described in this protocol.

7.3 Imaging Agent (ICG)

Systemic ICG, which is administered intravenously, is associated with some risks. ICG contains sodium iodide and should be used with caution in patients who have a history of allergy to iodides or iodinated imaging agents. Anaphylactic or urticarial reactions have been reported in patients with and without history of allergy to iodides. Anaphylactic deaths have been reported following ICG administration during cardiac catheterization[14,15].

Radioactive iodine uptake studies should not be performed for at least 1 week following ICG administration[14,15].

Animal reproduction studies have not been conducted with ICG. It is not known whether ICG can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. It

is not known whether ICG is secreted in human milk. Women who are pregnant or lactating are excluded from this study.

Subjects will most likely be administered ICG through a central line routinely placed for standard of care. Should a peripheral line be placed solely for the purpose of ICG intravenous administration, risks associated with intravenous injection include pain, bruising, ecchymosis, thrombosis, hematoma, infection, infiltration and/or extravasation.

8 STUDY PROCEDURES

8.1 Schedule of Events

Table 1 presents the schedule of events for this study.

PILLAR III

TABLE 1. Schedule of Events

Procedure	Baseline (Day -30 to Day 0)	Day 0 (Operative Phase)			Post-Operative Follow-Up			
		Pre-Op	Intra-Op	Post-Op	Day 1 (24±12 hrs.)	Date of Discharge[a]	Ileostomy Endoscopy/ Contrast Enema (Week 3 to Week 8 ±14d)	Week 8 (56±14d)
Informed consent	X							
Demography	X							
Vital signs, height, weight	X							
Surgical risk factors	X							
Pre-operative diagnosis	X							
Pregnancy test (record in source only)	X							
Inclusion/exclusion criteria	X							
Serum sodium, bilirubin, creatinine and INR for MELD Score	X							
Hemoglobin, Albumin, Pre-albumin		X	X[c]		X			
Randomization (in OR, during anesthesia)			X					
LAR surgical procedure			X					
Imaging agent administration (treatment group only)			X					
Perfusion Assessment (Perfusion arm only) Proximal transection margin Mucosal aspect of completed anastomosis			 X X					
Document actual surgical technique				X				
Anastomotic leak assessment				X	X	X		X
Surgical Complication assessment/grading			X	X	X	X		X
Endoscopy and/or contrast enema - Ileostomy subjects (between 3 & 8 wks.)							X[b]	
Concomitant medications and procedures	X	X	X	X	X	X		X
Adverse events/adverse device effects		X	X	X	X	X		X[d]

[a] Subjects with a discharge date later than Week 8, who did not have an ileostomy, will be followed until Week 8 ±14d.
[b] All subjects with a diverting ileostomy must have endoscopy and/or contrast enema between 3 weeks post-surgery and the Week 8 visit.
[c] Hemoglobin measurement at time of anastomosis if subject had any hypotensive events or blood loss over 500 ml at time of anastomosis[d] All subjects with adverse events thought to be related to the LAR procedure or the PINPOINT or SPY Elite system will be followed until resolution or deemed chronic.

8.2 Baseline/Screening Procedures (Day -30 to Day 0)

After signing the informed consent form, subjects will be assigned a screening number (see Section 5.2) and be evaluated for eligibility into the study.

The following procedures will be conducted during the baseline assessment:

- Collection of demographics, surgical risk factors, pre-operative diagnosis.
- Vital signs (heart rate and blood pressure), height and weight.
- Serum tests (bilirubin,sodium,creatinine and INR) for MELD Score

  The following online calculator from the OPTN website should be used to calculate the MELD Score:

  - https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/
- Pregnancy test (urine test or institution standard of care) for females of childbearing potential.

8.3 Day 0 Procedures

On Day 0, the following will be completed before randomization and surgery:

- Serum hemoglobin, prealbumin, and albumin measurement.

During anesthesia, subjects will be randomized as described in Section 5.1. Subjects are considered enrolled upon randomization.

According to the randomization assignment, subjects in the PERFUSION arm will receive perfusion assessment with PINPOINT and/or SPY Elite during surgery and undergo surgery according to the surgeon's standard practice. Subjects randomized to the Standard arm will undergo the surgery according to the surgeon's standard practice only. All subjects will receive the hospital/institution and surgeon's standard pre-operative and post-operative care with the addition of any study specific requirements. The LAR will be performed according to guidelines from the American Society of Colorectal Surgeons (ASCRS) to minimize variability. The LAR procedure may include the following:

- Circular stapled or transanally hand sewn anastomosis
- Open or minimally invasive low anterior resection
- Minimally invasive with or without hand-assist low anterior resection.
- Minimally invasive with or without open-assist low anterior resection.
- Conversion to open procedures.
- Transabdominal and/or transanal total mesorectal excision.
- Colorectal or coloanal reconstruction with or without reservoir/pouch.
- Ileostomy as required.

An intra-operative measurement of hemoglobin should be performed at the time of anastomosis if the subject experiences a hypotensive event requiring intraoperative management (e.g. use of vasopressors) or blood loss greater than 500 ml at the time of anastomosis.

Either during or immediately post-operatively, the details of the surgery will be documented. The following elements must be included and recorded in the Operative case report form (CRF):

- Actual procedure at start of operation/time of randomization
    - Occurrence of intra-operative conversion to open operation. Defined as the occurrence of an unplanned incision or an incision made longer or earlier than planned to facilitate dissection or mobilization. The use of a limited laparotomy wound to facilitate a low stapled anastomosis and/or specimen extraction is permissible and not defined as an open conversion.
- Level of inferior mesenteric artery (IMA) and vein (IMV) ligation.
    - High (proximal to left colonic take-off), mid (just distal to left colic takeoff) or low (colon marginal vessels).
- Final level of anastomosis from the anal verge (determined by assessing the markings on the stapler or by rigid proctoscopy at the discretion of the surgeon).
- Site of the proximal anastomosis segment (descending, sigmoid or transverse colon).
- Use of pelvic drains (yes or no).
- Ileostomy procedure performed or not performed.
- Revisions to the anastomosis.
- Criteria used to determine the point of proximal and distal transection.
- Criteria used in decision to divert.
- Occurrence of significant intra-operative hypotension events (e.g. use of vasopressors).
- Results of air leak test.
- Assessment of proximal and distal anastomotic donut (for completeness).
- Assessment of PINPOINT and/or SPY Elite to provide visualization of blood flow.
- Concomitant medications and procedures as described in Section 7.2.
- Adverse events according to Section 9.

8.3.1 ASCRS Guidelines for LAR

In order to minimize variability in the surgical approach, clinical guidelines from the ASCRS will be followed. Any deviations from the ASCRS guidelines will be recorded in the Intraoperative comments section of the Operative CRF. Refer to ASCRS Practice Parameters for the Management of Rectal Cancer (revised) for more detailed guidelines[19].

The following guidelines are recommended:

- A surgical exploration involving a thorough assessment of the peritoneal cavity and abdominal organs to detect or rule out synchronous lesions, advanced malignant disease or coexisting pathology.
- Total mesorectal excision for tumors of the middle and lower thirds of the rectum, and tumor-specific mesorectal excision extending at least 5 cm below the distal margin of the tumor for tumors of upper third of the rectum.
- For most rectal cancers, a 2-cm distal mural margin with a total mesorectal excision is adequate and a 1-cm distal mural margin is acceptable for cancers located at or below the mesorectal margin.
- Proximal vessel ligation at origin of superior rectal artery and resection of all associated lymphatic drainage

- In absence of clinical involvement, an extended lateral lymph node dissection in addition to TME is not necessary.
- Definitive resection should be offered to subjects with an apparent complete clinical response to neoadjuvant therapy.
- Intraoperative anastomotic leak testing should be performed.
- A diverting ostomy should be considered for subjects undergoing a TME for rectal cancer.
- Routine prophylactic oophorectomy is not necessary, but oophorectomy is advised for grossly abnormal ovaries or contiguous extension of a rectal cancer.
- Adjuvant chemoradiotherapy is recommended for subjects with stage III or high-risk stage II rectal cancer who have not received neoadjuvant therapy.
- Adjuvant chemoradiotherapy is recommended for subjects with stage III or high-risk stage II rectal cancer previously treated with neoadjuvant therapy.
- Surgical report should include information regarding the diagnostic workup, intraoperative findings, and technical details of procedure.

8.3.2 Perfusion Assessment

Subjects randomized to the PFN Arm will receive intraoperative imaging using PINPOINT or SPY Elite NIR fluorescence imaging to assess colon tissue perfusion of proximal transection margin after IMA ligation; prior to transection.

Subjects randomized to the PFN Arm will also receive intraoperative imaging using PINPOINT endoscopic fluorescence imaging to assess perfusion of the mucosal aspect of the completed anastomosis (with the exception of coloanal anastomosis when applicable).

Subjects randomized to the PFN Arm may receive additional intraoperative imaging or repeat imaging based on the surgeon's judgment.

At the completion of the procedure, an assessment regarding the ability of the PINPOINT or SPY Elite system to provide sufficient visualization for assessment of blood flow and related tissue perfusion will be made by the surgeon for subjects in the PFN Arm.

8.3.2.1 Imaging Agent Dosing and Administration

The ICG solution will be prepared and administered by the appropriate qualified study and/or operating room personnel. Refer to Chapter 4, Handling and Preparation and Administration of ICG in the PINPOINT and SPY Elite Operator's Manual for complete detailed instructions.

The dose for imaging of the proximal colon is 3.0 ml ± 1.0 ml of a 2.5 mg/ml concentration of ICG. The amount of ICG administered may be adjusted within this range to allow for surgeon preference for brightness. Additional imaging studies may be performed within minutes, once the blood volume of ICG from the initial injection has reached a concentration that will not interfere with the subsequent images. The plasma half-life of ICG is approximately 1-3 minutes. It is possible that subsequent doses of ICG may need to be reduced for the additional imaging studies. The dose for transanal imaging of the completed anastomosis is 3.0 ml ± 1.0 ml of a 2.5 mg/ml solution of ICG. Transanal imaging after anastomosis may require a lower dosage of ICG,

depending on residual fluorescence from previous imaging.

ICG is administered as a tight bolus through a peripheral or central intravenous (IV) line in order to ensure that the total dose of ICG is infused into the circulation as quickly as possible. It is important that the ICG bind to the plasma proteins in the blood as rapidly as possible to provide a clear, bright, useful image.

This is followed immediately by a 10 ml saline flush. The flush ensures rapid infusion of the imaging agent into the circulation. Opening an IV to flush is not an adequate substitute for a bolus injection of the flush solution. For optimum fluorescence imaging, the IV tubing needs to be cleared of any imaging agent as quickly as possible.

8.3.2.2 Proximal Transection Margin

At the point of the procedure when the colon/rectum has been mobilized and dissected fully and appropriately, the distal rectal transection has been completed, the IMA and IMV have been ligated, and the surgeon is prepared for proximal resection and subsequent low anastomosis, perfusion assessment will be performed.

Perfusion assessment of the proximal transection margin may be made with PINPOINT or SPY Elite depending on Investigator preference and approach (open vs minimally invasive).

The location of proximal transection will be based on clinical judgment and will include consideration of the following factors:

- A minimum distance of 5 cm from the tumor for the proximal resection margin.
- Sufficient bowel length to ensure a tension-free anastomosis.
- Preservation of bowel length.
- Adequate blood supply through visual inspection and palpation using the following assessment techniques where appropriate:
    - pink tissue with 1-2 second refill.
    - bleeding (bright red) from the cut edge or from abrasion or stabbing with needle.
    - presence of blood in bowel vasculature.

ICG will be administered and the surgeon will assess perfusion of the tissue around (proximal and distal to) the planned transection margin.

Perfusion imaging of the proximal transection margin may be performed intracorporeally or extracorporeally depending on Investigator preference. If proximal imaging is performed extracorporeally, all fluorescent lights must be turned off to minimize background noise.

The PINPOINT imaging head will be positioned between 5 cm and 30 cm (~2-12 inches) from the planned transection margin with the camera head positioned parallel to the area being imaged and planned transection margin centered in the field of view. The area being imaged must remain in focus throughout the imaging procedure.

If the Investigator chooses to utilize SPY Elite for proximal imaging, the following procedure will be followed. The SPY Elite Imaging head will be positioned parallel to the proximal colon, approximately 30 cm (~12 inches) from the bowel, with the proximal transection margin centered

in the field of view. SPY Elite imaging may be performed for proximal transection margin imaging in open procedures or for extracorporeal minimally invasive procedures.

When positioning is complete, the subject will receive an intravenous injection of ICG followed by an injection of saline flush solution. The dose and time of injection will be recorded. The image sequence will be recorded from the point of administration of saline flush, through the ICG wash-in, perfusion assessment and final point of proximal transection

Perfusion at the planned point of transection will be characterized as follows:

Inadequate – the absence of fluorescence, or spotty and/or patchy areas of green fluorescence.

Adequate – pale, dull, or faded green fluorescence.

Optimal – vivid, bright green fluorescence that entirely saturates the area of interest.

Proximal transection should be made within the area of optimal perfusion (bright fluorescence) when possible, with consideration given to the factors for determining the location of proximal transection detailed above. An imaging guide will be provided to all investigators to serve as a guideline for the interpretation of perfusion images. The clinical reasons for choosing the transection point will be recorded.

8.3.2.3 Anastomosis

Perfusion of the proximal and (where appropriate) distal sides of the mucosal aspect of the completed anastomosis will be assessed using PINPOINT only. The distal assessment will be performed after the standard air leak test (when performed) has been completed (air leak test can be omitted in hand sewn coloanal anastomoses). In the case of a hand sewn coloanal anastomosis, the assessment will involve assessment of the mucosal aspect of the proximal colon only.

The PINPOINT endoscope will be inserted into the anus via the Novadaq disposable rigid scope introducer (DRSI) provided as part of the PINPOINT Procedure Kit. Refer to the current version of the **Instructions for Use** for a full description of the DRSI[21]. The PINPOINT scope will be advanced to the point of the anastomosis under white light. The PINPOINT imaging head will be positioned approximately 5- 15 cm (~2-6 inches) from the completed anastomosis. The area being imaged must remain in focus throughout the imaging procedure. Sufficient insufflation is required for adequate assessment. ICG will be administered and the surgeon will assess the perfusion on the proximal and distal sides of the staple or suture line as inadequate, adequate or optimal. The flow sequence (proximal vs distal first) will also be recorded. The image sequence will be recorded from the ICG wash-in to perfusion assessment.

Note that it is important to image all portions of the completed anastomosis. If a colonic j-pouch or end to side anastomosis has been done, imaging and perfusion assessment may need to be performed intracorporeally as well as following completion of the anastomosis to ensure visualization of perfusion of all at risk areas (i.e., the entire conduit in the case of a pouch).

Additional imaging studies should be completed as necessary and the image sequences recorded.

Similar to perfusion imaging of the proximal bowel, perfusion of the mucosal aspect of the anastomosis will be characterized as follows:

Inadequate – the absence of fluorescence, or spotty and/or patchy areas of green fluorescence

Adequate – pale, dull or faded green fluorescence.

Optimal – vivid, bright green fluorescence that entirely saturates the area of interest

Refer to the perfusion imaging guide for guidance on interpretation of perfusion images.

A diverting ostomy will be based on clinical judgment in conjunction with perfusion assessment of the anastomosis. A diverting ostomy should be considered for all anastomoses located less than 7 cm to the anal verge. A diverting ostomy should be performed for all anastomoses with poor perfusion located less than 7 cm to the anal verge.

At the completion of the procedure, an assessment regarding the ability of the PINPOINT and SPY Elite (if applicable) system to provide sufficient visualization for assessment of blood flow and related tissue perfusion will be made by the surgeon.

8.4 Post-operative Follow-up Visits (Day 1 to Last Study Visit)

Subjects will have standard of care assessments throughout the study according to the hospital/institutions standard procedures as well as study specific visits on postoperative Day 1, the date of discharge, Week 8 (56 ±14 days) and the date of ileostomy closure, if applicable. Subjects will be assessed for the following throughout the study:

- Serum hemoglobin measurement (Day 1).
- Evidence of anastomotic leak.
- Assessment and grading of post-operative complications.
- Concomitant medications and procedures as described in Section 7.2.
- Adverse events according to Section 9.

Although the patient may be seen by various individuals post-surgery, the study-specific visits must be conducted by a surgeon who is part of the study and has signed the Signature and Delegation Log. Any complications and outcomes of study required assessments between visits will be documented at the study required visits.

Subjects with a discharge date later than Week 8, who did not have an ileostomy, will have the last study visit on Week 8 ±14 days.

Diverted patients should receive routine endoscopic and/or contrast enema evaluation of the anastomotic region, between 3 weeks post-surgery and the Week 8 visit.

Subjects who present with a clinical suspicion of anastomotic leak during the study will have a CT scan with PO and, if necessary (e,g., presence of a diverting ileostomy), rectal contrast to confirm.

8.5 Image Acquisition and Transmission

Videos of the image sequences acquired using PINPOINT and SPY Elite will be recorded to a medical grade video recorder. All required images will be provided to the Sponsor by the Investigative Center. Image files will be identified using the subject I.D. number and initials only (no information identifying the subject shall be included in the files).

9 EVALUATION, RECORDING, AND REPORTING OF ADVERSE EVENTS

All untoward medical occurrences either observed by the Investigator or one of his/her medical collaborators, or reported by the subject spontaneously, or in response to the direct question below, will be reported as follows:

- All events occurring before randomization should be recorded in the source documents and will be considered part of the subject's case history.
- Events occurring as a result of the surgery will be reported as adverse events related to the surgical procedure in the adverse event CRF.
- All adverse events occurring during the study will be recorded as adverse events on the adverse event CRF.
- Events related to the use of PINPOINT or SPY Elite will be recorded as adverse device effects in the description of event section of the adverse event CRF.
- Events related to PINPOINT or SPY Elite that affect a user of the device (non-patient) are recorded on the technical complaint form.

In an attempt to optimize consistency of AE reporting across centers, the subjects must be asked a standard question to elicit events. At each clinic evaluation of the subject, study personnel will ask the following questions: "Have you had any problems since your last visit?"

AEs reported on the CRF will include the date of onset, severity, relationship to PINPOINT or SPY Elite, relationship to surgical procedure, date of resolution (or the fact that it is ongoing or has become chronic), action taken, and whether the AE is serious or not.

9.1 Definitions

9.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory findings) in subjects whether or not related to the investigational medical device.

- Includes events related to the PINPOINT or SPY Elite.
- Includes events related to procedures involved (any procedure in the clinical investigation plan).
- Postoperative nausea or vomiting occurring during the first 24 to 48 hours, and post-

operative pain related to surgical procedure is not considered an adverse event.

9.1.2 Adverse Device Effect (ADE)

Any adverse event related to the use of PINPOINT or SPY Elite (includes imaging agent and all hardware components).

- Includes any event that is a result of a use error or intentional misuse.

ADEs that affect subjects will be recorded as ADEs in the AE CRF. ADEs that only affect a user (non-patient) are recorded in the technical complaint form only.

9.1.3 Serious Adverse Event (SAE)

Any adverse event that:

a. Led to a death.

b. Led to a serious deterioration in health that either:

   i. Resulted in a life-threatening illness or injury,

   ii. Resulted in a permanent impairment of a body structure or a body function,

   iii. Required in-patient hospitalization or prolongation of existing hospitalization,

   iv. Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

c. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

This includes device deficiencies that might have led to a serious adverse event if suitable action had not been taken; intervention had not been made, or if circumstances had been less fortunate. These are handled as SAEs. A planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in heath, is not considered to be a serious adverse event.

9.1.4 Unanticipated Adverse Device Effect (UADE)

Any ADE that meets the following:

- By its nature, incidence, severity or outcome has not been identified in the current version of the PINPOINT (or SPY Elite if applicable) risk analysis report.

- On health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9.2 Adverse Event Descriptions

9.2.1 Intensity

The intensity of AEs, including ADEs and surgical complications will be characterized as mild, moderate, or severe, as follows:

Mild	Usually transient, requiring no special treatment, and does not interfere with the subject's daily activities.
Moderate	Introduces a low level of inconvenience or concern to the subject and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.
Severe	Significantly interferes with a subject's usual daily activities and requires systemic drug therapy or other treatment, if available.

9.2.2 Relationship

Suspected	There is a reasonable possibility that the AE is associated with use of the study device, such as temporal relationship of the event to use.
Not suspected	A relationship between the AE and the study device can reasonably be ruled out based on lack of any temporal relationship of the event to use, or when the subject's underlying condition, medical history, or other therapy provide sufficient explanation for the observed event.

9.3 Reporting and Evaluation of Serious Adverse Events and Unanticipated Adverse Device Effects

Any SAE or UADE occurring in this study must be reported immediately (within 24 hours of discovery) by email to the Novadaq contact listed below:

Attention: Alicia Wilton

Phone: 905-629-3822 x209Email : pillar3@novadaq.com

SAEs and UADEs will be reported to the Institutional Review Board (IRB)/Ethics Committee (EC) according to the institution's policies, but within 10 days of occurrence.

The Sponsor will provide documentation of reportable events to the Investigator, as specified in Section 13.1.4.

The Investigator will ensure that the subject receives appropriate medical treatment and that the subject is followed up until the SAE or UADE resolves or becomes chronic, as defined in Section 9.5.

9.4 Surgical Complications: Special Instructions

Anastomotic leaks, and strictures or abscesses that require intervention should be reported and followed as SAEs for this study.

Subjects who present with a clinical suspicion of anastomotic leak during the study will have a computerized tomography (CT) scan to confirm unless the patient's condition warrants urgent operative intervention. A leak is considered confirmed if endoluminal contents (air, gastro-intestinal contents or contrast material) through the anastomosis occur. The presence of infection or abscess thought to be related to the anastomosis may be classified as an anastomotic leak at the surgeon's discretion even if it cannot be definitively identified as visualized during an operation or by contrast extravasation. An abscess adjacent to the anastomosis containing air will be classified as a leak. All Anastomotic leaks will be followed until resolution.

Specific post-operative complications are defined as follows for this study and should be reported as surgical complications and SAEs if they meet SAE criteria at the time of the event:

- Prolonged post-operative NPO or nasogastric tube (NGT) use is defined as prolonged NPO status or NGT use for more than 3 post-operative days (POD4 or later), or the return to NPO status or insertion(or presence) of NGT anytime POD4 or later within 30 days.

- Post-operative ileus is defined as insertion or reinsertion of a NGT after surgery or a return to NPO status for nausea and/or vomiting with failure of passage of flatus and/or stool.

- A small bowel obstruction is defined as radiologic or operative evidence of an obstruction.

All adverse events and post-operative complications occurring during the study period will be graded according to the following Clavien-Dindo classification system[20] as shown in Table 2. Grades will be recorded on the CRF.

TABLE 2. Classification of Surgical Complications

Grade	Definition	Clinical Example of Complication Grade
Grade I	Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions	Non-infectious diarrhea
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.	Infectious diarrhea requiring antibiotics
Grade IIIa	Requiring surgical, endoscopic or radiological intervention not under general anesthesia	Radiologic or endoscopic intervention of an anastomotic leak that is taken care of outside of the operating room
Grade IIIb	Requiring surgical, endoscopic or radiological intervention under general anesthesia	Surgical intervention of an anastomotic leak that is taken care of in the operating room
Grade IVa	Life-threatening complication (including CNS complications)[a] requiring IC/ICU management with single organ dysfunction (including dialysis)	Necrotizing pancreatitis
Grade IVb	Life-threatening complication (including CNS complications)[a] requiring IC/ICU management with multi organ dysfunction	Necrotizing pancreatitis with hemodynamic instability
Grade V	Death of a patient	Organ failure after surgical intervention-
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.	

[a] Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks

9.5 Follow-up for Adverse Events and Adverse Device Effects

Throughout the study to the final study visit contact, ADEs will be followed until they resolve or become chronic. All AEs will be followed throughout the study until the Week 8 visit. All AEs related to the PINPOINT, SPY Elite or the surgical procedures, as determined by the Investigator, will be followed until resolution or deemed chronic.

At the final study visit, new AEs, as well as follow-up information for continuing AEs, will be recorded in the CRF and source document. If an SAE or UADE is unresolved at the final study visit, it will be followed by the Investigator until it resolves or becomes chronic (as judged by the Investigator). Follow-up data for such SAEs will be recorded in the source document and reported to the safety contacts. Non-serious ongoing AEs will be followed beyond the final study visit at the discretion of the Investigator.

9.6 Reporting of Technical Complaints/Device Deficiencies

9.6.1 Definitions

Device Complaint: A quality complaint received in writing, electronically, or orally that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device product. (In this definition, "effectiveness" refers to the actual function of the device, not to how the subject responds to the action of the device. Also in this definition, "device product" refers only to devices provided by the Sponsor for clinical studies and to investigational devices.)

In this definition, safety includes the safety of a subject, user, or other person associated with the use of a medical device.

Device Deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labeling.

9.6.2 Reporting Procedures

Any technical complaint/device deficiency should be reported to the Sponsor. Technical Complaints occurring in this study must be reported immediately (within 24 hours) by fax or email to the appropriate Novadaq representative or to Novadaq Quality (quality@novadaq.com).

Any complaint about a device must be reported regardless of whether the defect or deficiency had any effect on a subject or on study personnel.

9.7 ADEs, Technical Complaints/Device Deficiencies that are UADEs

Novadaq will evaluate all ADE reports and technical complaints/device deficiencies to determine if the report meets the definition of an unanticipated adverse device effect. If Novadaq determines that it does meet the definition, an investigation will be begun immediately. Novadaq will inform the Investigator of any additional reporting requirements beyond those stated in Sections 9.3 and 9.7 as applicable.

Novadaq will report the UADE and the results of any investigations to the FDA. All participating Investigator(s) will submit the required reports to their IRBs within 10 working days after Novadaq first received notice of the effect.

10 STATISTICAL CONSIDERATIONS

10.1 Primary Objective

To demonstrate an improvement in post-operative anastomotic leak rate in low anterior resection procedures where colon and rectal tissue perfusion is evaluated using PINPOINT or SPY Elite near infrared fluorescence imaging as an adjunct to standard surgical practice compared to surgical procedures performed according to standard surgical practice alone.

10.2 Hypotheses

H_0: $p_t = p_c$
H_1: $p_t < p_c$

Where p_t and p_c represent the expected population incidences of post-operative anastomotic leaks in the treatment (PERFUSION) and control groups, respectively. Within their respective treatment groups, p_t and p_c will be estimated as the number of subjects who experience a post-operative anastomotic leak according to the definition in Section 3.1, divided by the number of subjects who either are included in the numerator or are known to be free of such leaks as of the 8 weeks visit. Subjects without a known anastomotic leak but with less than 6 weeks of follow-up (i.e., insufficient follow-up to declare them "leak-free") will not be included in these estimates.

10.3 Statistical Analysis

Analysis of these hypotheses will be conducted using a z-test (i.e., normal approximation to the binomial distribution, using a pooled variance estimate and without continuity correction), using a (one-sided) significance level of 0.025.

10.4 Adaptive Design and Sample Size Considerations

Available literature does not provide a precise estimate of the expected anastomotic leak rate in the control group or in the treatment group. As previously described, anastomotic leak is reported to occur in a wide range of 3-20% of the time in colorectal surgery[6-10] and the risk increases for lower anastomoses. In the limited prior experience with the PINPOINT PILLAR II study (n=139 subjects) the anastomotic leak rate was 1.4%.

Given the limited knowledge of control incidence and the treatment effect size, the PILLAR III study will employ an adaptive design with a mid-trial sample size re-assessment. The planned sample size is N = 800, with possible early stopping for efficacy or futility at an interim analysis at N = 450. The planned total of 800 subjects will provide >80% power to test the one-sided hypothesis of superiority for treatment over control in leak rate at the 0.025 significance level if the true leak rates p_c and p_t are 12.5% and 6.25% (a 50% relative reduction), assuming a two-look group sequential analysis plan (with Pocock alpha-spending bounds and analyses at 450 and 800). If the trial does not stop at N = 450, sample size will be assessed at that time and possibly increased up to a maximum of 1000 subjects, using the method of Chen et al.[23] and described in Mehta and Pocock[22].

For the primary objective, the following analysis plan will be used After N = 450 subjects have been enrolled, randomized and treated and the primary outcomes observed. The primary objective null hypothesis will be tested against the one-sided alternative hypothesis above. If $p < 0.0169$ (as determined by the Pocock alpha spending function), the null hypothesis will be rejected, whereas if $p \geq 0.4$, the trial will be considered futile However, if $0.0169 \leq p < 0.4$an assessment of whether to increase the sample size above the planned 800 subjects will be made in accordance with the "promising zone" method of Mehta and Pocock. If the conditional power (CP) at N =800 subjects based on the available data at the time of the interim analysis is less than 0.5 or at least 0.8, enrollment will continue to 800 subjects and the final analysis will be conducted. Alternatively, if $0.5 \leq CP < 0.8$, the sample size will be re-estimated in accordance with the Mehta and Pocock method for sample size re-estimation up to a maximum of 1000 subjects. (The re-calculated sample size cannot be less than 800 subjects based on the interim analysis.) The final sample size is calculated by determining the added sample size needed to achieve the target conditional power of 80% given the data at the time of the interim analysis, subject to a maximum of 1000 subjects. This method guarantees control of the type I error while still allowing standard inferential methods of analysis.

10.5 The planned sample size 800 . is based on the following rationale: If the true leak rates p_c and p_t are 12.5% and 6.25% (a 50% relative reduction), respectively,then PASS 13 [24] indicates that , a two-look group sequential analysis plan (with Pocock alpha-spending bounds and analyses at 450 and 800) achieves 81.6% power to reject the null hypothesis at a one-sided significance level of 0.025. Study Populations for Analysis

10.5.1 Modified Intent-to-Treat (mITT)

The mITT analysis population includes all randomized subjects in whom a low anterior resection surgical procedure is initiated or at least one injection with ICG was performed. All subjects meeting these criteria are included in the mITT population, regardless of whether or not they received the planned open, or minimally invasive surgical intervention or NIR fluorescence imaging assessment using the PINPOINT or SPY Elite device. Subjects who have the surgical resection procedure aborted due to circumstances such as a higher stage cancer than initially anticipated will not be included in the mITT population. Subjects will be analyzed according to their randomized group assignment. The mITT population is the analysis population for both the primary and secondary endpoints.

10.5.2 As-Treated (AT)

The As-Treated (AT) analysis population includes all randomized subjects in whom the intended open, or minimally invasive low anterior resection surgical procedure and, if assigned to the PERFUSION arm, PINPOINT or SPY Elite NIR fluorescence imaging with at least one perfusion assessment using ICG was successfully performed. Subjects in whom the intended surgical procedure is not performed or imaging with PINPOINT or SPY Elite was not successful are excluded from the AT population. mITT subjects not included in the AT population will be followed in the same manner as mITT subjects who do meet AT population inclusion criteria. Subjects will be analyzed according to the treatment actually received.

The AT population will be used for a secondary analysis of the primary endpoint.

10.5.3 Per-protocol (PP)

The Per-protocol (PP) population will consist of all AT subjects that: [1] meet critical study eligibility criteria; [2] have no significant protocol deviations; and [3] have evaluable assessment for the primary study endpoint.

The PP population will be used for subset analysis of the primary endpoints.

10.6 Safety (S)

The safety analysis population includes all randomized subjects. Secondary safety endpoints including the summary of adverse events in the trial will be analyzed using this analysis population, divided into groups according to actual use or non-use of PINPOINT and SPY Elite.

10.7 Secondary Objectives

The planned secondary objectives are listed below; they will be formally analyzed only once (at the interim analysis if the primary objective is passed at that time, or at the final analysis if the primary objective is not passed at the interim analysis). Data from these secondary objectives will not be included in the sample size re-assessment that occurs at the time of the interim analysis.The following objectives are intended to support product labeling. They will be tested in sequential fashion. I.e., if and only if the primary objective passes according to the criteria in Section 10.5 (which has a type I error rate of 2.5%), testing will proceed to the first secondary objective below (proportion of PERFUSION arm subjects in whom the PINPOINT or SPY Elite system provided sufficient visualization for assessment of blood flow and related tissue perfusion during the procedure). If and only if that objective passes, testing will proceed to the second secondary objective (incidence of abscess requiring surgical management). The standard for "passing" the secondary objectives will be a p-value less than 0.025 one sided.

To evaluate the ability of the PINPOINT or SPY Elite system to provide sufficient visualization for assessment of blood flow and related tissue perfusion during the procedure.

The statistical threshold for study success will be sufficient visualization for assessment of blood flow and related tissue perfusion in greater than 90% of subjects. Letting pt represent the PERFUSION-group proportion of subjects for whom there was sufficient visualization for assessment of blood flow and related tissue perfusion, the following hypotheses will be tested:

H0: $p_t \leq 0.9$

H1: $p_t > 0.9$

The statistical test will be a one-sided exact binomial test of proportions. Descriptive statistics and 95% confidence intervals will be calculated for p_t.

To evaluate the effectiveness of assessing perfusion of colon and rectal tissue using PINPOINT or SPY Elite in reducing the incidence of post-operative abscess requiring surgical management.

Letting p_t and p_c respectively represent the treatment-group and control-group incidence of post-operative abscess requiring surgical management, the following hypotheses will be tested:

H_0: $p_t = p_c$

H_1: $p_t < p_c$

The statistical test will be a z-test using pooled variance estimate and no continuity correction. In the case of small counts, an exact procedure will be used. Descriptive statistics and 95% confidence intervals will be calculated for p_t, p_c, and ($p_t - p_c$).

10.8 Handling of Missing Data

Reasonable efforts will be made to obtain complete data for all patients; however, missing observations will inevitably occur due to patients lost to follow-up or noncompliance with required assessments. The reasons for missing data will be documented and evaluated (e.g. patient is deceased, lost to follow up, missed visit, etc.). In addition, the distribution of prognostic factors between patients with data and those without data will be examined to evaluate any potential sources of bias. Any missing observations will be described in detail and evaluated for assessment of possible bias. The planned sensitivity analyses for the primary outcome in the primary analysis population (including a tipping point analysis which addresses the worst case scenario in which treatment group subjects with missing observations are considered failures and control group subjects with missing observations are considered successful) is described in further detail in the Statistical Analysis Plan (SAP).

10.9 Pooling of Site Data

The homogeneity of safety and effectiveness results across study sites will be examined and if no significant heterogeneity is found, the results will be pooled. The justification for pooling is that all study sites will follow one Protocol, use the same device system (PINPOINT or SPY Elite), follow the same Instructions for Use and perform surgery in accordance with surgical guidelines from ASCRS. Additionally, frequent contact and monitoring of the sites will be performed to ensure that all Study sites are evaluating participants and recording Study results in a reliable and reproducible manner. It is not anticipated that any individual Study site will dominate the Study results. Therefore, it is believed that these procedures will help to ensure that the data from these Study sites can be combined and analyzed as if generated at a single site. Further explanation on poolability analyses, including testing baseline factors and the handling of significant site interactions, is described in the SAP.

11 ESTIMATED DURATION OF THE STUDY

The expected study duration is approximately 2.5 years. The study is expected to start in the first half of 2015 and take approximately 24 months to complete enrollment.

12 STUDY ETHICAL CONSIDERATIONS

12.1 Ethical Conduct of the Study

The study will be conducted in accordance with US 21 CFR Part 812 and US 21 CFR Parts 50, 54, and 56. Any additional requirements imposed by the local Institutional Review Board/Ethics Committee/Research Ethics Board or regulatory agency will be followed as necessary.

12.2 Informed Consent

The informed consent forms used for the study must comply with applicable laws and regulations. An Investigator must explain the medical aspects of the study, including the nature of the study and procedure, orally and in writing, in such a manner that the subject is aware of potential benefits and risks. Other elements of the informed consent process may be delegated by the Investigator. Subjects must be informed about all aspects of the clinical study that are necessary to make the decision to participate in the clinical trial. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Documentation of the discussion and the date of informed consent must be recorded in the source documentation. Subjects must give informed consent in writing.

The informed consent process must be conducted, and the form must be signed, before the subject undergoes any screening procedures that are performed solely for the purpose of determining eligibility for the study.

12.3 Institutional Review Board, Ethics Committee, or Research Ethics Board (IRB)

The protocol, protocol amendments (as specified by the IRB), and the informed consent form for the proposed study, along with any other documents required by the center's IRB must be submitted by the Investigator to the center's duly constituted IRB for review and approval. The Investigator must also ensure that the IRB reviews the progress of the study on a regular basis and, if necessary, renews its approval of the study on an annual basis. A copy of each IRB approval letter must be forwarded to the Sponsor before the study is implemented. Documentation of subsequent reviews of the study must also be forwarded to the Sponsor.

13 ADMINISTRATIVE PROCEDURES

13.1 Sponsor's Responsibilities

13.1.1 Public Disclosure of Clinical Trials

The Sponsor will submit information about this protocol to the appropriate web-based national clinical trial registry and results database in each applicable regulatory region where the study is conducted. This includes but is not limited to the US National Institute of Health (www.clinicaltrials.gov). The Sponsor will update the information, including any changes to the study or recruitment status throughout the study.

13.1.2 Study Supplies

The Sponsor will provide the PINPOINT Endoscopic Fluorescence Imaging System and if requested, the SPY Elite Intraoperative Imaging System along with sufficient quantities of PINPOINT Procedure Kits with Introducer and SPY PAQs.

13.1.3 Investigator Training

13.1.3.1 Study Initiation Visit

Study centers will have a study initiation meeting to ensure the research personnel understand the protocol, study requirements, and data capture processes. This training will take place prior to enrollment of the first subject at each study center.

13.1.3.2 PINPOINT and SPY Elite System

Appropriate personnel at the study centers shall be required to participate in training on the procedural use of PINPOINT and SPY Elite as it relates to the conduct of this study (refer to Section 6.1 and Section 6.2).

13.1.4 Ongoing Communication of Safety Information During the Study

The Sponsor will provide the Investigator with documentation of UADEs and reportable events/effects, from all study centers, reported to regulatory authorities during the conduct of the study. The Investigator must forward this documentation to the IRB, as described in Section 9.3.

The Sponsor will also notify the Investigator about any other safety findings that could affect the safety of subjects, affect the conduct of the study, or alter the IRB's opinion about continuation of the study.

13.1.5 Study Monitoring

The conduct of the study will be monitored by representatives of the Sponsor to ensure compliance with the protocol, GCP and applicable regulations. A separate study specific Monitoring Plan will outline the monitoring procedures to be followed, the required access to source data and the extent of source verification planned.

13.1.6 Records Retention

The Sponsor must retain all documentation pertaining to the study according to Novadaq standard operating procedures.

13.2 Investigator's Responsibilities

13.2.1 Reporting and Recording of Study Data

Data will be captured and compiled using procedures developed by the Sponsor or their representatives. All requested study data must be recorded clearly on the CRF and other study forms as required. An explanation should be provided for all missing data. Only individuals who are identified on the Study Signature and Delegation Log may enter or correct data in the CRF. Incomplete or inconsistent data on the CRFs will result in data queries that require resolution by the Investigator.

The protocol, informed consent form, protocol amendments, safety information, and other required documents must be submitted to the IRB in a timely manner, as described in Section 12.3.

13.2.2 Source Documentation

The Investigator must maintain adequate and accurate source documents upon which CRFs for each subject are based. They are to be separate and distinct from CRFs, except for cases in which the Sponsor has predetermined that direct data entry into specified pages of the subject's CRF is appropriate. These records should include detailed notes on:

- The oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). The date of informed consent must be recorded in the source documentation.
- The subject's basic identifying information, such as demographics, that links the subject's source documents with the CRFs.
- All relevant observations and data on the condition of the subject throughout the study.
- The subject's exposure to PINPOINT and SPY Elite.
- All adverse events.

13.2.3 Study Devices

The Investigator is responsible for ensuring the PINPOINT system and SPY Elite system, including imaging agent, is controlled and is used or dispensed only to subjects enrolled in the study. Only Investigators identified on the Signature and Delegation Log may use PINPOINT and SPY Elite for the purposes of this study.

The Investigator shall keep records documenting the receipt, use, return and disposal of the study device and components.

The Investigator will ensure that PINPOINT and SPY Elite is returned and that any other study material will be returned to the Sponsor or disposed of according to the Sponsor's instructions on completion of the study.

13.2.4 Records Retention

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 Sponsor immediately if any documents are to be destroyed, to be transferred to a different facility, or to be transferred to a different owner.

13.3 Data and Safety Review

A Data and Safety Monitoring Committee (DSMC) has been established by the Study Sponsor to oversee the safety and other aspects of the study. The DSMC will also be responsible for reviewing the interim analysis conducted by an independent statistician in conjunction with the Study Sponsor and/or the Sponsor's Delegates and advising the Study Sponsor on determining the sample size of Stage 2. The DSMC consists of two independent board certified colorectal surgeons and an independent biostatistician. Ad-Hoc members may be appointed if specific expertise is needed. The role of the DSMC is to provide independent oversight and ensure that the study is conducted according to currently established safety and ethical standards. The Sponsor will oversee the provision of data to the DSMC. In general, it is anticipated that the DSMC meets twice a year. The DSMC reviews and evaluates all SAEs, UADEs and outcome measures and also receives a summary report for all ADEs and non-serious AEs. Unless specific action is required, the results of the analyses reviewed by the DSMC will not be shared

with site investigators. The DSMC will also develop rules for stopping the study. The Study Sponsor will distribute DSMC summary reports to collaborating clinical sites for submission to the sites' IRB. A separate DSMC Charter will define monitoring procedures and stopping rules.

13.4 Independent CT/Contrast Enema Scan Assessment

An independent Radiologist will review CT/contrast enema scans for all subjects who present with a clinical suspicion of anastomotic leak during the study. The independent Radiologist's assessment will be the final determination recorded for the study database. A separate IR Charter will define the image acquisition, data management and image analysis procedures.

14 DATA MANAGEMENT

Study data will be collected using paper and/or electronic case report forms (CRFs). Data will be entered into a study specific database in one of two ways or a combination of the following:

- Center research personnel will enter study data directly into an electronic case report form which functions as an electronic data capture screen for the study database.

- Center research personnel will enter study data onto paper CRFs, which will be submitted to the Sponsor or assigned designee.

The Sponsor or designee will follow standardized procedures for data review, database cleaning and issuing/resolving queries. Procedures for data verification, validation, security and data retention will be followed in order that the study data reported are complete, accurate and consistent with source data.

For the purpose of data analysis and presentation, the data of the original data set may be manipulated and additional variables calculated when necessary. Once the study data are completely entered, reviewed and checked, the study database will be locked and no further changes will be made.

15 POLICY FOR PUBLICATION AND PRESENTATION OF DATA

The results of the study will be published by the PILLAR III Study Group (PSG). In addition to overall principal investigator, additional authors listed separately on the manuscript will be selected based on scientific input on the design of the study, interpretation of results, participation in manuscript preparation and on enrollment numbers. The final number of authors will depend on the journal's publication guidelines. All participating centers will be acknowledged in the main study manuscript.

The Sponsor also encourages the scientific publication of data from clinical research studies. However, Investigators may not present or publish partial or complete study results individually without participation of the study Principal Investigator as well as the Sponsor. The Principal Investigators and the Sponsor may propose appropriate scientific manuscripts or abstracts from the study data. All proposed publications must be reviewed and commented on by the Sponsor before submission for publication. The detailed procedures for the review of publications are set out in the clinical trial agreement entered into with the Sponsor in connection with this study. These procedures are in place to ensure coordination of study data publication and adequate review of data for publication against the validated study database for accuracy. Names of all

Investigators and Sponsor representatives responsible for designing the study and analyzing the results will be included in the publication(s).

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