FILM-B

Clinical Study Protocol

PROTOCOL NUMBER
SPY LNM 01

TITLE
A Single Arm, Prospective, Open Label, Multicenter Study Assessing the Safety and Effectiveness of IC2000 and SPY **F**luorescence **I**maging Systems in the Visualization of Lymphatic Vessels and **L**ymph Nodes during Lymphatic **M**apping and Sentinel Lymph Node Biopsy in Subjects with **B**reast Cancer

SHORT TITLE
FILM-B

PROTOCOL VERSION
Version 7.0, August 13 2020

SPONSOR
Novadaq Technologies ULC, now a part of Stryker.

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Confidential

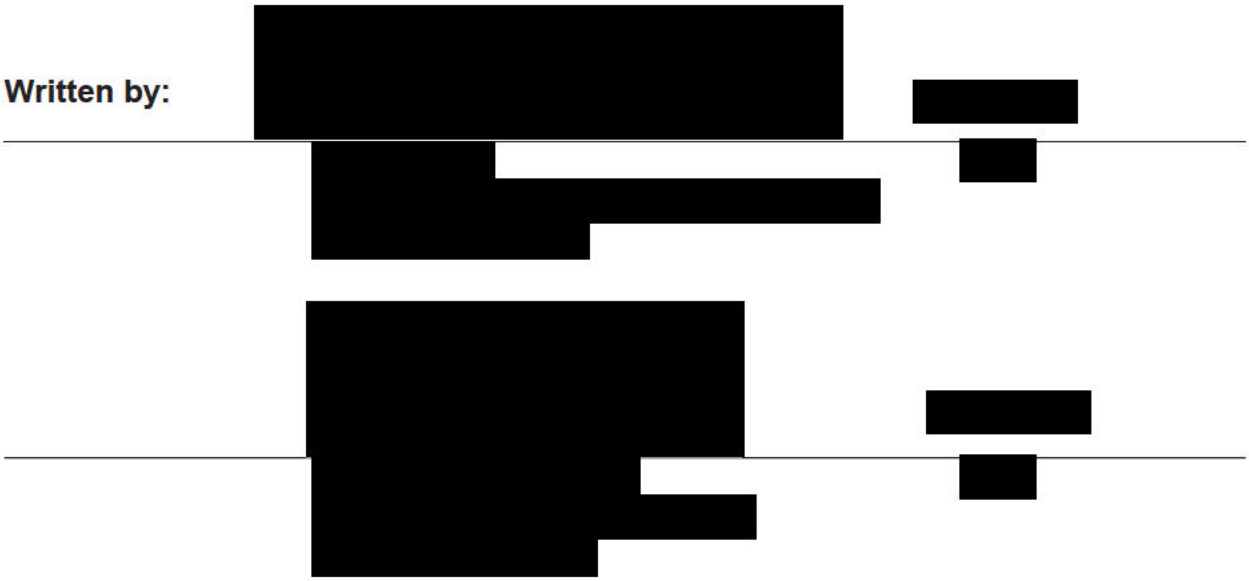
1. PROTOCOL APPROVALS

Protocol Number: SPY LNM 01

Title of Protocol: A Single Arm, Prospective, Open Label, Multicenter Study Assessing the Safety and Effectiveness of IC2000 and SPY Fluorescence Imaging Systems in the Visualization of Lymphatic Vessels and Lymph Nodes during Lymphatic Mapping and Sentinel Lymph Node Biopsy in Subjects with Breast Cancer

Version: 7.0, August 13, 2020

Written by:



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Version: 7.0, August 13, 2020

Approved by: [redacted]

Approved by: [redacted]

Approved by: [redacted]

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Version: 7.0, August 13, 2020

Approved by: [redacted]

Approved by: [redacted]

2. PROTOCOL SUMMARY

2.1 Study Number and Title

SPY LNM 01 (FILM-B): A Single Arm, Prospective, Open Label, Multicenter Study Assessing the Safety and Effectiveness of IC2000 and SPY Fluorescence Imaging Systems in the Visualization of Lymphatic Vessels and Lymph Nodes during Lymphatic Mapping and Sentinel Lymph Node Biopsy in Subjects with Breast Cancer

Clinical Phase*:* Phase III - Investigational Device Study

2.2 Study Objectives

Primary

- To assess the effectiveness of IC2000 and SPY-PHI (SPY Portable Handheld Imager; also called “IC2000 and SPY”) Fluorescence Imaging System in the identification of lymph nodes (histology confirmed lymph nodes), during lymphatic mapping and sentinel lymph node biopsy in subjects with early stage breast cancer.

Secondary

- To evaluate the effectiveness of IC2000/SPY and Tc99m/Gamma Probe in the identification of at least one lymph node (histology confirmed lymph node) per subject.
- To evaluate the effectiveness of IC2000 and SPY as an intraoperative fluorescence visualization tool in delineation and mapping of lymphatic vessels in the identification of lymph nodes (histology confirmed lymph nodes).
- To confirm the safety of intradermal injection of IC2000 in intraoperative delineation and mapping lymphatic vessels and identification of lymph nodes.

2.3 Study Design

This is a prospective, open label, multicenter, non-inferiority within-patient study to determine the effectiveness of IC2000 (Indocyanine Green (ICG) for Injection) and the SPY Portable Handheld Imaging System (SPY-PHI) as an intraoperative fluorescence visualization tool, in the visual identification of lymphatic vessels and lymph nodes (LNs) during lymphatic mapping and sentinel lymph node biopsy (SLNB) procedures as confirmed by Technitium99m (Tc99m) and Gamma Probe. Enrollment will not exceed 1[redacted] centers in North America. Prior to enrolling study subjects, participating surgeons at each center will be:

- Required to have completed a minimum of (5) lymphatic mapping and sentinel lymph node identification procedures using SPY-PHI with ICG.
    - Trained to perform the intradermal injection technique with ICG.

Screening

Subjects diagnosed with breast cancer with either Ductal Carcinoma in Situ (DCIS) (Stage 0, T_{is}, N0, M0) or clinical stage IA, IB or IIA[1] who are scheduled for surgery that includes clinically indicated SLNB with Tc-99m radioactive colloid and Gamma Probe will be included to determine if they meet the inclusion/exclusion criteria (Note: Only subjects who subsequently consent to undergo LN mapping and identification using IC2000 and SPY-PHI as an intraoperative fluorescence visualization tool may be enrolled in the study – see below for details).

Subjects will be evaluated at baseline to determine if they meet the inclusion/exclusion criteria of the FILM-B protocol. Subjects considered for inclusion in the study will be assessed to determine overall health status including demographics, vital signs, diagnosis and relevant medical history/underlying conditions.

Day 0

As per standard of care, all subjects will receive an injection of Tc-99m radioactive colloid either the day before or the morning of surgery[1]. On the day of surgery subjects will receive an injection of IC2000 at the start of surgery while the subject is in the operating room and under anesthesia. The injection will occur prior to SLNB as IC2000 and SPY will be used to map and identify LNs for excision.

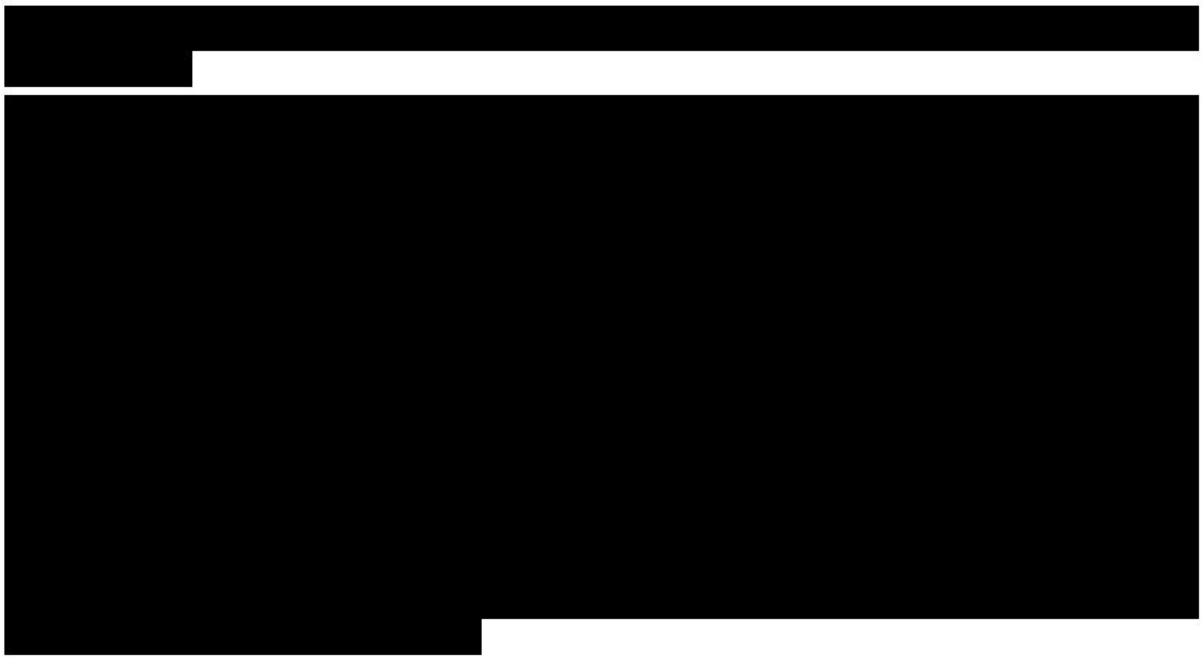
The breast(s) identified with DCIS or stage IA, IB or IIA cancer will be injected with IC2000 (2.5 mg/ml solution) in the peri-areolar area as described below.

[redacted]

Visual Identification, Mapping Procedure and LN Excision:

Following the intradermal peri-areolar injection of IC2000, the surgeon will intraoperatively map the lymphatic vessels from the injection site in order to identify the LNs based on intraoperative fluorescence visualization using IC2000 and SPY-PHI. Imaging will commence by tracing the lymphatic vessels from the point of

[redacted]



Clinically suspicious LNs designated as palpable masses will be excised regardless of visible fluorescence or if deemed 'hot' with a gamma probe.

Classification of LNs:

All LNs identified by IC2000/SPY-PHI and Tc99m/Gamma Probe will be classified *ex-vivo or in-vivo* by the surgical investigator:

1. Fluorescent only
2. Tc99m only
3. Both (Fluorescent and Tc99m positive)
4. Clinically suspicious (Fluorescence and Tc99 negative)

Failed mapping is defined as no LNs detected either by Tc99m and Gamma Probe, IC2000 and SPY or LNs deemed clinically suspicious.

Details of the surgery, including intraoperative findings will be documented. Surgical data will be documented on study specific case report forms (CRFs).

Follow-up and Post-Operative Complications

Subjects will have standard of care assessments throughout the study according to the hospital / institution's standard procedures. Subjects will be monitored for the occurrence of any adverse events/adverse device effects on the date of discharge and on Day 30 (±7 days).

[redacted]

2.4 Study Population

To be eligible for the study, subjects must meet the following main inclusion criteria:

- 18 years of age or older.
- Subjects with American Cancer Society Clinical Stage 0 Ductal Carcinoma in Situ (DCIS) (Stage 0, T_{is}, N0, M0), IA (T1*, N0, M0), IB ((T0, N1mi, M0) or T1*, N1mi, M0)) or Stage IIA (T0, N1**M0, or T1, N1**, M0 or T2, N0, M0)[1] breast cancer undergoing surgery to remove tumor draining LNs.

  Where:

  - T_{is} = Ductal carcinoma in situ
  - T0 = No evidence of primary tumor
  - T1 = Tumor ≤ 20 mm in greatest diameter
  - T1* = Includes T1mi
  - T2 = Tumor >20 mm but ≤ 50 mm in greatest diameter
  - N0 = No regional lymph node metastasisq1`
  - N1 = Metastasis to movable ipsilateral level I, II axillary LNs
  - N1** = T0 and T1 tumors with nodal micro-metastasis only are excluded from Stage IIA and are classified Stage IB.
  - mi = Micro-metastasis
  - M0 = Disease has not metastasized
- Subjects with clinically negative nodal status (N0) with or without neoadjuvant therapy.
- Subjects with negative metastatic involvement (M0).
- Subjects of child-bearing potential must not be pregnant or lactating and must have a negative pregnancy test at Baseline.
- Have signed an approved informed consent form for the study.
- Be willing to comply with the protocol.

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

- Have had prior axillary surgery or ipsilateral radiation in the breast(s) that is planned for this procedure.
- Advanced breast cancer subjects with stage IIB, III or IV.
- Known allergy or history of adverse reaction to ICG, iodine or iodine dyes.
- Subjects who have participated in another investigational study within 30 days prior to surgery.
- Pregnant or lactating subjects.

- Subjects who, in the Investigator's opinion, have any medical condition that may make the subject a poor candidate for the investigational procedure, or interferes with the interpretation of study results.

2.5 Study Devices and Imaging Agents

In this study, IC2000 and SPY-PHI will be assessed as an intraoperative fluorescence visualization tool in the identification of LNs during lymphatic mapping in subjects undergoing sentinel lymph node biopsy with early stage breast cancer.
SPY-PHI is intended for intraoperative visual assessment of blood vessels and related tissue perfusion by surgeons. It is an imaging system used in capturing and viewing fluorescent images for visual assessment of blood flow, as an adjunctive method for the evaluation of tissue perfusion, and related tissue-transfer circulation in tissue and free flaps during various surgical procedures.

SPY-PHI allows for real time, intraoperative visualization and video of near infrared (NIR) fluorescence, which are acquired by using the imaging agent.

The imaging agent used with SPY-PHI is Indocyanine Green (IC2000), which is a sterile, water-soluble tricarbocyanine dye with a peak spectral absorption at 800-810 nm in blood plasma or blood. IC2000 contains not more than 5.0% sodium iodide. In this study, investigational ICG, IC2000, will be administered to subjects through an intradermal injection into the peri-areolar area of the breast.

Tc-99m radioactive colloid injection is a clear, colorless aqueous solution and will be injected into the peri-areolar area of the breast as per standard of care.

Tc99m will be used in conjunction with the Gamma Probe. Gamma Probes detect the presence of gamma rays emitted from radioactive isotopes in body organs or tissue . The system provides an increasing or decreasing sound and visual indicator (Count Bar) that vary in pitch as level of gamma radioactivity increases or decreases[3].

2.6 Study Variables

Primary Variable

- To assess the effectiveness of IC2000 and SPY-PHI (SPY Portable Handheld Imager; also called “IC2000 and SPY”) Fluorescence Imaging System in the identification of lymph nodes (histology confirmed lymph nodes), during lymphatic mapping and sentinel lymph node biopsy in subjects with early stage breast cancer.
    - Defined as the proportion of lymph nodes identified and excised by IC2000/SPY compared to the proportion of lymph nodes identified and excised by Tc99m/Gamma Probe, (histology confirmed lymph nodes). Denominator is the total number of lymph nodes identified and excised, inclusive of clinically suspicious lymph nodes (histology confirmed).

Secondary Variables

- To evaluate the effectiveness of IC2000/SPY and Tc99m/Gamma Probe in the identification of at least one lymph node (histology confirmed lymph node) per subject.
    - Defined as the proportion of subjects in which at least one lymph node is identified by IC2000/SPY, and Tc99m/Gamma Probe, (histology confirmed lymph nodes). Numerator is the number of subjects who have at least one lymph node identified by IC2000/SPY, and the number of subjects who have at least one lymph node identified by Tc99/Gamma Probe, respectively (histology confirmed). Denominator is the total number of subjects where mapping was attempted.
- To evaluate the effectiveness of IC2000 and SPY as an intraoperative fluorescence visualization tool in delineation and mapping of lymphatic vessels in the identification of lymph nodes (histology confirmed lymph nodes).
    - Defined as the proportion of lymph nodes identified by IC2000 and SPY (histology confirmed lymph nodes) by following a fluorescent lymphatic vessel compared to the proportion of lymph nodes identified by IC2000 and SPY (histology confirmed lymph nodes) with no lymphatic vessels visible by IC2000 and SPY. Denominator is the total number of lymph nodes identified by any method (histology confirmed).
- To confirm the safety of intradermal injection of IC2000 in intraoperative delineation and mapping lymphatic vessels and identification of lymph nodes.
    - Defined by the incidence of adverse events with IC2000.

2.7 Study Procedures and Assessments

The following assessments and procedures will be performed:

- Vital signs, height, weight, demographics, surgical predictive factors.
- Relevant medical history and underlying conditions.
- Assessment of eligibility criteria.
- Tc-99m radioactive colloid administration.
- Imaging agent (IC2000) administration.
- Mapping of lymphatic vessels using IC2000 and SPY-PHI.
- Identification of lymph nodes using IC2000 and SPY-PHI
- Excision of lymph nodes identified with IC2000 and SPY-PHI
- Confirmation and/or identification of lymph nodes with Tc-99m radioactive colloid and Gamma Probe *ex-vivo* and *in-vivo*.
    - LNs identified *in-vivo* by Tc99 and Gamma Probe will be excised under visual guidance of IC2000 and SPY.

- Clinically suspicious LNs designated as palpable masses will be excised.
- Failed mapping will be documented.
- Documentation of lymphatic mapping and SLNB procedure.
- Classification of excised lymph nodes.
- Histological assessment of all excised lymph nodes.
- Concomitant medications.
- Assessment of surgical complications.
- Adverse events and adverse device effects.
    - Follow-up visits will occur on the date of discharge, and Day 30. Subjects with a discharge date later than Day 30 will have their last study visit on Day 30.

2.8 Sample Size and Statistical Analysis

This is a prospective, open label, multicenter, non-inferiority within-patient study to determine the effectiveness of IC2000 (Indocyanine Green (ICG) for Injection) and the SPY Portable Handheld Imaging System (SPY-PHI) as an intraoperative fluorescence visualization tool, in the visual identification of lymphatic vessels and LNs including LNs during lymphatic mapping and SLNB procedures as confirmed by Tc99m and Gamma Probe. A sample size of 356 LNs contributed by approximately 137 evaluable patients will be required using the following assumptions:

1. The average detection rate with Tc99m and Gamma Probe will be 91.6%.
2. The average detection rate with IC2000 and SPY will be 96%.
3. A power of 90%.
4. A non-inferiority margin of 5 percentile units.
5. An average of 2 LNs is expected to be excised per patient.

Estimating that 6% of patients will be excluded from the per-protocol (PP) population (see section 14.1), approximately 379 LNs are required.

Additional details are included in Section 14.7, Sample Size Considerations.

2.9 Study Duration

[redacted]

3. TABLE OF CONTENTS

4. ABBREVIATIONS AND DEFINITIONS

ADE	Adverse Device Effect
AE	Adverse Event
ALND	Axillary Lymph Node Dissection
ASBrS	American Society of Breast Surgeons
AT	As-treated
BD	Blue Dyes
CFR	Code of Federal Regulations
CRF	Case Report Form
DCIS	Ductal Carcinoma In-Situ
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
H&E	Hematoxylin and Eosin
HD	High Definition
HSA	Human Serum Albumin
IA	Imaging Agent
IB	Isosulfane Blue
ICH	International Conference on Harmonization
ICG	Indocyanine Green
IRB	Institutional Review Board
LN	Lymph Node
MB	Methylene Blue
mITT	Modified Intent-to-treat
NIR	Near-Infrared
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SLN	Sentinel Lymph Node
SLNB	Sentinel Lymph Node Biopsy
SPY	SPY Fluorescence Imaging Systems
SPY-PHI	SPY-PHI Open Field Handheld Fluorescence Imaging System
Tc99m	Technetium 99m
Tc99m – TM	Technetium 99m – Tilmanocept
Tc99m – SC	Technetium 99m – Sulfur Colloid
US	United States
UADE	Unanticipated Adverse Device Effect
VIS	Visible

5. 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.

5.1 Background

The purpose of this study is to assess the safety and effectiveness of using IC2000 and SPY-PHI as an intraoperative fluorescence visualization tool of lymphatic vessels and identification of lymph nodes (histology confirmed LN detected by IC2000 and SPY) during lymphatic mapping and sentinel lymph node biopsy (SLNB) in subjects with early stage breast cancer.

[redacted]

5.1.1 Breast Cancer

[redacted]

[redacted]

5.1.2 Intraoperative Lymphatic Mapping and Lymph Node Identification

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.2 Potential Risks and Benefits to Human Subjects

In this study, IC2000 and SPY-PHI will be assessed as an intraoperative fluorescence visualization tool in the identification of lymphatic vessels and lymph nodes (histology confirmed LNs detected by IC2000 and SPY-PHI) during lymphatic mapping in subjects undergoing sentinel lymph node biopsy with early stage breast cancer.

The device does not have diagnostic capabilities. The surgeon / user retains the ultimate responsibility for making the pertinent diagnosis based on their standard practice and visual comparison of the separate images obtained.

SPY-PHI is classified by the United States FDA as a Class II medical device with a Product Code of OWN. SPY-PHI has a 510(k) clearance from the FDA (K200737) for the following indications for use:

> *"Upon intravenous administration of SPY AGENT™ GREEN (indocyanine green for injection, USP) the SPY-PHI System is used with SPY AGENT™ GREEN to perform intraoperative fluorescence angiography. The SPY-PHI System is indicated for use in adult and pediatric patients one month of age and older.*
>
> *The SPY-PHI System is indicated for fluorescence imaging of blood flow and tissue perfusion before, during, and after: vascular, gastrointestinal, organ transplant, and plastic, micro- and reconstructive surgical procedures.*
>
> *Upon interstitial administration of SPY AGENT™ GREEN, the SPY-PHI System is used to perform intraoperative fluorescence imaging and visualization of the lymphatic system, including lymphatic vessels and lymph nodes."*

SPY-PHI is also licensed in Canada as a class 2 medical device with the following intended use:

> *Upon intravenous administration of SPY AGENT™ GREEN (Indocyanine green for injection, USP) the SPY-PHI System is used with SPY AGENT™ GREEN to perform intraoperative fluorescence angiography.*
>
> *The SPY-PHI System is indicated for fluorescence imaging of blood flow and tissue perfusion before, during, and after: vascular, gastrointestinal, organ transplant, and plastic, micro- and reconstructive surgical procedures.*
>
> - *Examples of its use for near-infrared fluorescence imaging before, during and after various procedures include, but are not limited to, coronary bypass surgery, organ transplant procedures, plastic and reconstructive surgery such as breast reconstructive procedures and micro-surgery (including plastic reconstructive surgery utilizing autologous flaps), renal cancer surgeries, vascular surgeries (such as wound, amputation and coronary vessels), myocardial perfusion in cardiac and cardiovascular surgeries, GI surgeries and parathyroid perfusion during endocrine surgery.*

The risks of the SPY-PHI system in humans are described further in Section 11, Risks / Precautions. For detailed information, please refer to the SPY-PHI Operator's Manual[38].

[redacted]

The imaging agent ICG, is approved for use in humans by the FDA and Health Canada. In this study, investigational ICG (IC2000) will be administered intradermally and used with SPY-PHI as an intraoperative fluorescence visualization tool in the identification of

LNs (histology confirmed LN detected by IC2000 and SPY) during SLNB. [redacted]

These and other risks of ICG in humans are described further in Section 11, Risks/Precautions. For additional information, please refer to the commercial ICG Package Insert[45].

6. STUDY OBJECTIVES

6.1 Objectives

Primary

- To assess the effectiveness of IC2000 and SPY-PHI (SPY Portable Handheld Imager; also called "IC2000 and SPY") Fluorescence Imaging System in the identification of lymph nodes (histology confirmed lymph nodes), during lymphatic mapping and sentinel lymph node biopsy in subjects with early stage breast cancer.

Secondary

- To evaluate the effectiveness of IC2000/SPY and Tc99m/Gamma Probe in the identification of at least one lymph node (histology confirmed lymph node) per subject.
- To evaluate the effectiveness of IC2000 and SPY as an intraoperative fluorescence visualization tool in delineation and mapping of lymphatic vessels in the identification of lymph nodes (histology confirmed lymph nodes).
- To confirm the safety of intradermal injection of IC2000 in intraoperative delineation and mapping lymphatic vessels and identification of lymph nodes.

7. INVESTIGATIONAL PLAN

7.1 Study Design Overview

This is a prospective, open label, multicenter, non-inferiority within-patient study to determine the effectiveness of IC2000 (Indocyanine Green (ICG) for Injection) and the SPY Portable Handheld Imaging System (SPY-PHI), as an intraoperative fluorescence visualization tool in the visual identification of lymphatic vessels and identification of LNs during lymphatic mapping and SLNB procedures as confirmed by Tc99m and Gamma

Probe. Enrollment will not exceed 190 subjects at up to 10 centers in North America. Prior to enrolling study subjects, participating surgeons at each center will be:

- Required to have completed a minimum of (5) lymphatic mapping and sentinel lymph node identification procedures using SPY-PHI with ICG.
- Trained to perform the intradermal injection technique using ICG.

7.2 Screening

Subjects diagnosed with breast cancer with either Ductal Carcinoma in Situ (DCIS) (Stage 0, Tis, N0, M0) or clinical stage IA, IB or IIA who are scheduled for surgery that includes clinically indicated SLNB with Tc-99m radioactive colloid and Gamma Probe (Note: Only subjects who subsequently consent to undergo LN mapping and identification using IC2000 and SPY-PHI as an intraoperative fluorescence visualization tool may be enrolled in the study).

Subjects will be evaluated at baseline to determine if they meet the inclusion/exclusion criteria of the FILM-B protocol. Subjects considered for inclusion in the study will be assessed to determine overall health status including demographics, vital signs, diagnosis and relevant medical history/underlying conditions.

7.3 Day 0

Eligible subjects who have provided informed consent will be enrolled in the study on Day 0. The surgical procedure will be performed according to the surgeons and/or institutions standard practice.

7.3.1 Intraoperative Lymphatic Mapping and Lymph Node Identification

As per standard of care, all subjects will receive an injection of Tc-99m radioactive colloid either the day before or the morning of surgery[2]. On the day of surgery subjects will receive an injection of IC2000 at the start of surgery while the subject is in the operating room and under anesthesia. The injection will occur prior to SLNB as IC2000 and SPY will be used to map and identify LNs for excision.

The breast(s) identified with DCIS or stage IA, IB or IIA cancer will be injected with IC2000 (2.5 mg/ml solution) in the peri-areolar area as described below.

[redacted]

[redacted]

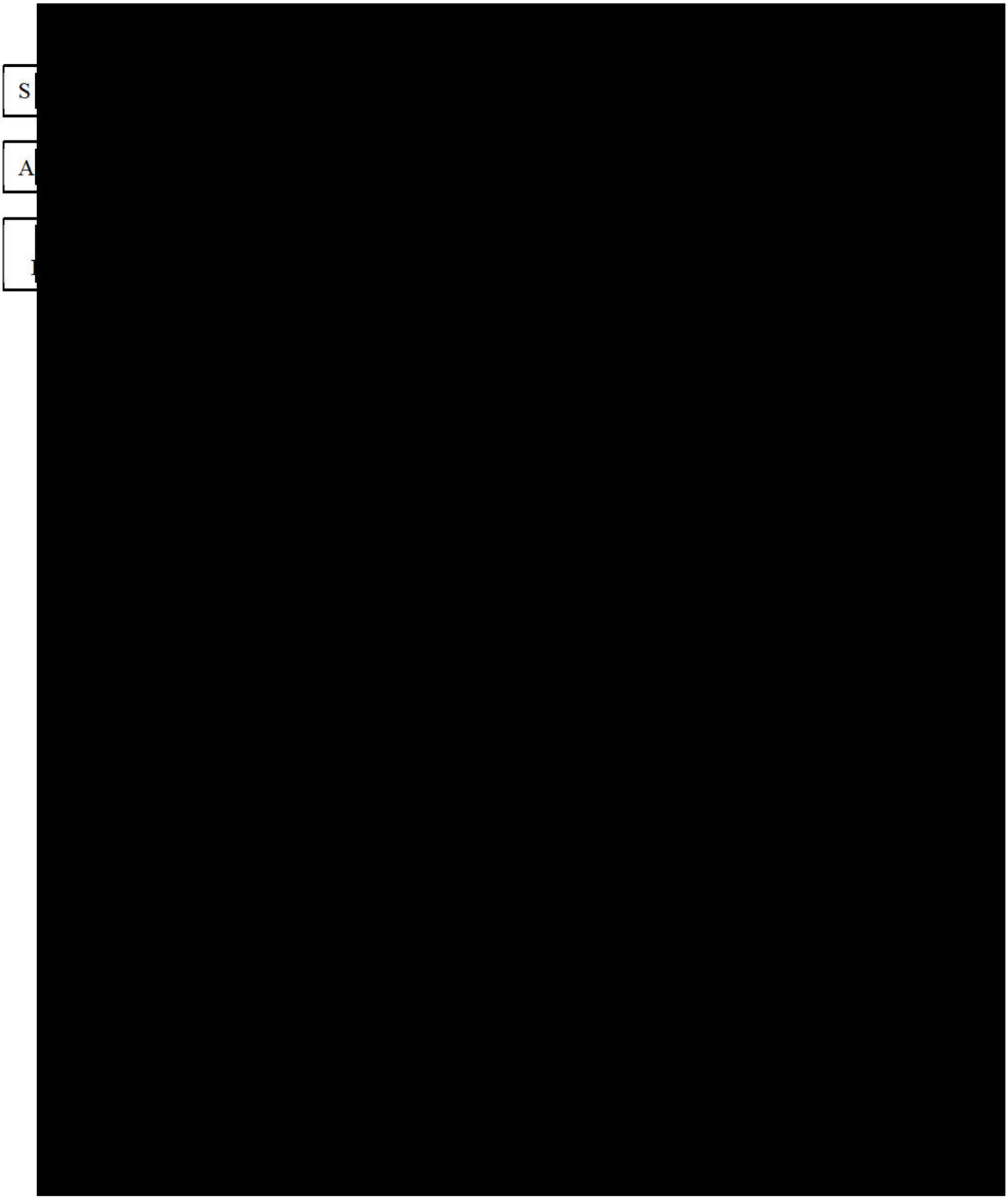
7.4 Classification of LNs

[redacted]

7.5 Follow-up and Post-operative Complications

All subjects will have standard of care assessments throughout the study according to the hospitals/institution's standard procedures. Study specific visits will monitor the occurrence of any adverse events/adverse device effects (AEs/ADEs) on the date of discharge and Day 30 (±7 days). All adverse events will be followed up to Day 30 (±7 days). Adverse events thought to be related to the use of IC2000, SPY, Tc-99m radioactive colloid, or to the LN mapping procedure will be followed until resolution or deemed chronic. In addition, all concomitant medications will be recorded if taken to treat an AE, ADE, Serious AE (SAE) or unanticipated ADE (UADE).

The overall study design is shown below in Figure 1.



8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1 Number of Subjects

Enrollment in the study will not exceed [redacted].

8.2 Inclusion Criteria

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

- 18 years of age or older.
- Subjects with American Cancer Society Clinical Stage 0 Ductal Carcinoma in Situ (DCIS) (Stage 0, T_{is}, N0, M0), IA (T1*, N0, M0), IB ((T0, N1mi, M0) or T1*, N1mi, M0)) or Stage IIA (T0, N1**M0, or T1, N1**, M0 or T2, N0, M0)[1] breast cancer undergoing surgery to remove tumor draining LNs.

  Where:

  - T_{is} = Ductal carcinoma in situ
  - T0 = No evidence of primary tumor
  - T1 = Tumor ≤ 20 mm in greatest diameter
  - T1* = Includes T1mi
  - T2 = Tumor >20 mm but ≤ 50 mm in greatest diameter
  - N0 = No regional lymph node metastasis
  - N1 = Metastasis to movable ipsilateral level I, II axillary LNs
  - N1** = T0 and T1 tumors with nodal micro-metastasis only are excluded from Stage IIA and are classified Stage IB.
  - mi = Micro-metastasis
  - M0 = Disease has not metastasized
- Subjects with clinically negative nodal status (N0) with or without neoadjuvant therapy.
- Subjects with negative metastatic involvement (M0).
- Subjects of child-bearing potential must not be pregnant or lactating and must have a negative pregnancy test at Baseline.
- Have signed an approved informed consent form for the study.
- Be willing to comply with the protocol.

8.3 Exclusion Criteria

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

- Have had prior axillary surgery or ipsilateral radiation in the breast(s) that is planned for this procedure.
- Advanced breast cancer subjects with stage IIB, III or IV.
- Known allergy or history of adverse reaction to ICG, iodine or iodine dyes.
- Subjects who have participated in another investigational study within 30 days prior to surgery.
- Pregnant or lactating subjects.
- Subjects who, in the Investigator's opinion, have any medical condition that may make the subject a poor candidate for the investigational procedure, or interferes with the interpretation of study results.

8.4 Withdrawal of Subjects

Subjects can voluntarily withdraw (or be withdrawn) at any time during the study. Investigators may withdraw a subject from the study due to:

- 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 intolerable 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 relevant page of the subject's Study Completion CRF.

Subjects who discontinue the study prematurely will not be replaced. The Sponsor may stop the study at any time.

9. SUBJECT ENROLLMENT AND SUBJECT IDENTIFICATION PROCEDURES

9.1 Subject Enrollment

Enrollment will occur on the day of surgery. Prior to surgery, the subject will have provided written informed consent, completed all baseline procedures and met all the requirements of inclusion and exclusion. Enrollment should be performed as closely as possible to the surgical procedure to minimize the incidence of dropout. Enrollment is completed only after verification of proper informed consent and study eligibility.

9.1.1 Subject Enrollment Procedure

Since this study is a single arm design, randomization is not required. In the FILM-B study, each subject will serve as their own control. All subjects enrolled will receive the same study treatment, which is lymphatic mapping using IC2000/SPY-PHI and Tc99/Gamma Probe during sentinel lymph node biopsy. This will allow for a direct, non-inferiority comparison of IC2000 and SPY-PHI to Tc99 and Gamma Probe in lymphatic mapping and identification of LNs during SLNB in subjects with early stage breast cancer. The study coordinator or designee will verify that the subject is eligible and that informed consent has been obtained prior to initiating the enrollment process. Once complete, the study coordinator or designee will assign the subject an Enrollment ID Number and the subject will be considered enrolled in the trial. The study coordinator will then disclose to the Investigator that the enrollment process is complete.

A subject cannot receive study treatment until the enrollment process has been completed. The enrollment procedure should not be initiated unless the study coordinator or designee verifies the baseline information and confirms that the subject is eligible. If any deviations occur (errors such as assigning incorrect enrollment), the clinical site will be required to contact the Sponsor and wait for guidance on how to proceed.

If, at any time after enrollment, the subject becomes ineligible or withdraws, the subject will be categorized with respect to the definitions outlined for the analysis populations (see Section 14, Statistical Methods).

9.2 Subject Identification

10. STUDY TREATMENTS

10.1 Device Descriptions

10.1.1 SPY Portable Handheld Imaging (SPY-PHI) System

SPY-PHI is an imaging system used in capturing and viewing fluorescent images for the visual assessment of blood flow, as an adjunctive method for the evaluation of tissue perfusion, and related tissue-transfer circulation in tissue and free flaps used during various surgical procedures.

SPY-PHI consists of the following components:

- An Open Field Handheld Imaging Head (with an integrated Light Guide cable), and the Video Processor/Illuminator (VPI).
- SPY-PHI PAQs containing the imaging agent, Water for Injection or aqueous solvent, and sterile drapes

The SPY-PHI System provides full color visible light and NIR fluorescence video imaging for intraoperative visual assessment of blood vessels and related tissue perfusion.

SPY-PHI has a 510(k) clearance from the FDA (K200737) for the following indications for use:

"

Upon intravenous administration of SPY AGENT™ GREEN (indocyanine green for injection, USP) the SPY-PHI System is used with SPY AGENT™ GREEN to perform intraoperative fluorescence angiography. The SPY-PHI System is indicated for use in adult and pediatric patients one month of age and older.

The SPY-PHI System is indicated for fluorescence imaging of blood flow and tissue perfusion before, during, and after: vascular, gastrointestinal, organ transplant, and plastic, micro- and reconstructive surgical procedures.

Upon interstitial administration of SPY AGENT™ GREEN, the SPY-PHI System is used to perform intraoperative fluorescence imaging and visualization of the lymphatic system, including lymphatic vessels and lymph nodes."

SPY-PHI is also licenced in Canada with the following intended use:

Upon intravenous administration of SPY AGENT™ GREEN (Indocyanine green for injection, USP) the SPY-PHI System is used with SPY AGENT™ GREEN to perform intraoperative fluorescence angiography.

The SPY-PHI System is indicated for fluorescence imaging of blood flow and tissue perfusion before, during, and after: vascular, gastrointestinal, organ transplant, and plastic, micro- and reconstructive surgical procedures.

- *Examples of its use for near-infrared fluorescence imaging before, during and after various procedures include, but are not limited to, coronary bypass surgery, organ transplant procedures, plastic and reconstructive surgery such as breast reconstructive procedures and micro-surgery (including plastic reconstructive surgery utilizing autologous flaps), renal cancer surgeries, vascular surgeries (such as wound, amputation and coronary vessels), myocardial perfusion in cardiac and cardiovascular surgeries, GI surgeries and parathyroid perfusion during endocrine surgery.*

[redacted] Please refer to the SPY-PHI Operator's Manual for a full description and specifications of the system[38]. In this study, the use of IC2000 and SPY-PHI for visual identification of LNs is investigational.

[redacted]

10.2 Imaging Agent Description

10.2.1 IC2000 for Injection (ICG for Injection, USP)

[redacted]

[redacted]

10.2.1.3 Chemistry and Manufacturing

[redacted]

IC2000 was manufactured in full compliance with the FDA's current Good Manufacturing Practice (cGMP) for Finished Pharmaceuticals (21 CFR Part 211) and meets all cGMP requirements for Health Canada.

10.2.1.4 Labelling of IC2000

IC2000 is labeled according to US and Canadian regulatory requirements with the following information:

- IC2000 (indocyanine green for injection, USP), 25 mg lyophilized ICG
- Sterile
- Protocol No.: SPY LNM 01
- Directions for use: Refer to Clinical Protocol
- Store at: 20–25°C (68-77°F)
- Lot: xxxxxxxx
- EXP: Mmm-YYYY
- CAUTION - New drug - Limited by Federal (or United States) law to investigational use.
- Investigational drug to be used only by a qualified investigator.
- Sponsor: Novadaq Technologies ULC. 8329 Eastlake Drive, Unit 101, Burnaby, BC, Canada, V5A 4W2. 1.844.668.2327

10.2.1.5 Packaging and Distribution of IC2000

IC2000 will be packaged into investigational FILM-B SPY-PHI Cases which contain 6 SPY-PHI Kits as described below and distributed by the study Sponsor (NOVADAQ). Each FILM-B SPY-PHI Kit is indicated for use exclusively with the SPY-PHI System, and should only be used for the purposes of this study (see also Section 17.1.2, Study Supplies).

Each FILM-B SPY-PHI Kit contains:

- One single use 25 mg vial of sterile IC2000 for Injection, USP
- One single use 10 ml vial sterile Water for Injection
- One SPY-PHI Sterile Drape
- 10 ml syringes, sterile
- 1 ml Tuberculin syringe, sterile
- 30G, 0.75 inch needle, sterile

All information included on the IC2000 for Injection vial labels will appear on the FILM-B SPY-PHI Kit labels along with a description of the contents of the kit. Each kit will bear a unique serial number and will meet regulatory requirements necessary for each participating country.

10.2.1.6 Storage and Administration of IC2000

FILM-B SPY-PHI Cases and Kits which contain IC2000 will be stored at 20°C to 25°C (68° to 77°F) in a secure locked area, accessible to authorized personnel only. FILM-B SPY-PHI Cases and Kits will be stored, and the IC2000 will be handled, prepared and administered by qualified, trained personnel only as described in Section 12.3.2, Imaging Agent Dosing and Administration of IC2000.

10.3 Installation, Training and Storage

[redacted]

10.4 Concomitant Treatment

11. RISKS / PRECAUTIONS

Refer to the SPY-PHI Operator's Manual for a full description of the risks and precautions associated with all components of the SPY-PHI respectively. The entire SPY-PHI Operator's Manual should be read before using the device[38]. Failure to follow the instructions and warnings in the manual may result in unsafe operation of the system and/or injury to the subject or operator.

11.1 SPY-PHI System

SPY-PHI is classified by the United States FDA as a Class II medical device with a Product Code of OWN. SPY-PHI, for the purposes of fluorescence angiography, is not identified as a significant risk device on the FDA Information Sheet titled "Significant Risk and Non-significant Risk Medical Device Studies".

The use of the SPY-PHI for LN identification and mapping is investigational. SPY-PHI should only be used in accordance to their approved Indication for Use or in accordance to the study procedures described in this protocol.

11.2 IC2000 (Indocyanine Green for Injection, USP)

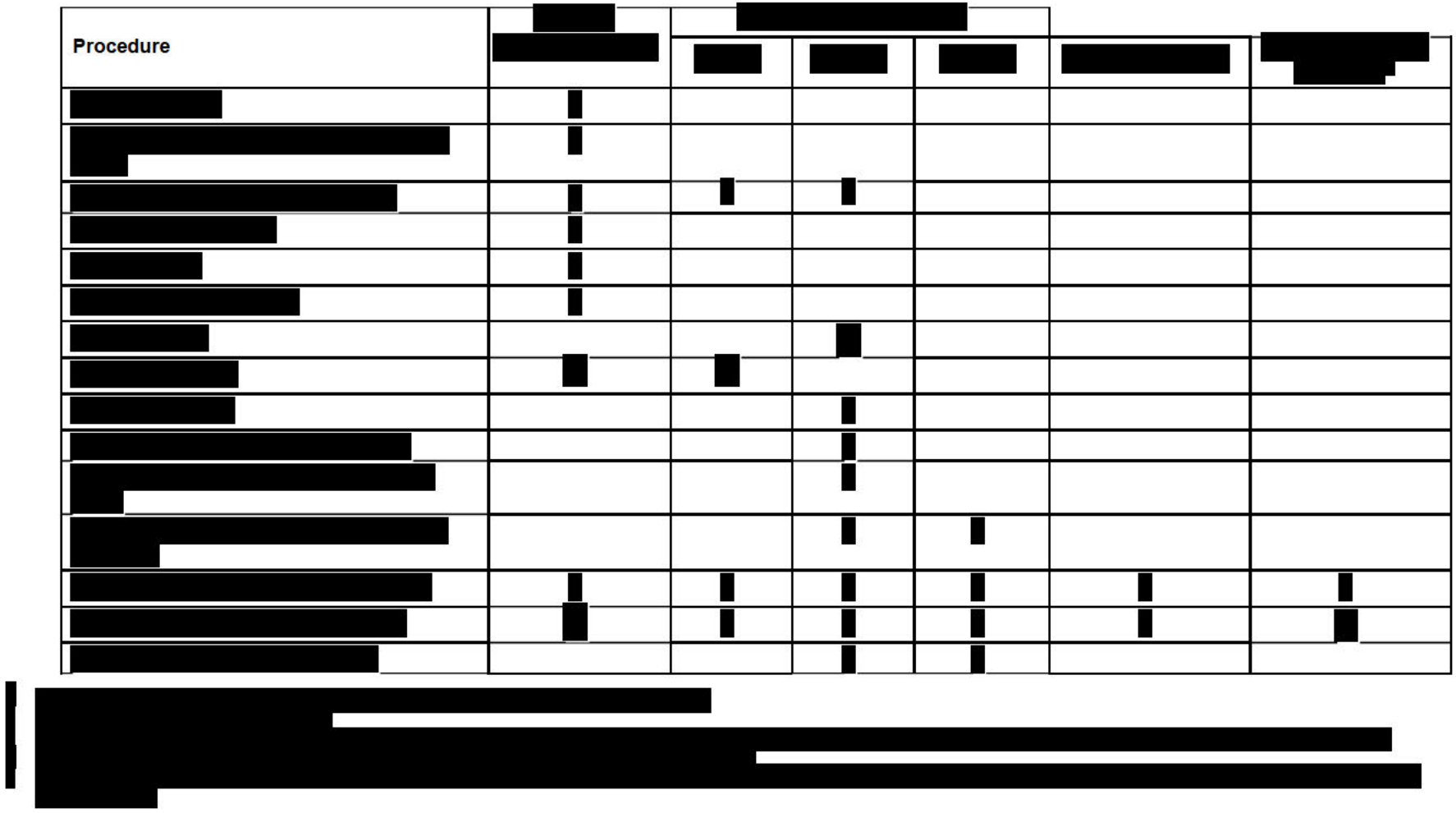
IC2000 will be injected intradermally into the peri-areolar area of the breast, and in subjects with occluded or blocked lymphatic vessels ICG will be injected intradermally

peri-tumorally. [redacted]

12. STUDY PROCEDURES

12.1 Schedule of Events

Table 3 Schedule of Events



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

After signing the informed consent form, subjects will be assigned a screening number (see Section 9.2, Subject Identification) and be evaluated for eligibility into the study.

The following procedures will be conducted during the baseline assessment:

12.3 Day 0 Procedures

As per standard of care, all subjects will receive an injection of Tc-99m either the day before or the morning of surgery.

Subjects are considered enrolled after verification of proper informed consent and eligibility, just prior to the time of injection of IC2000, at the start of surgery while the subject is in the operating room and under anesthesia (see below for administration procedures).

For mapping procedure details, refer to Section 7.3.1.2, Visual Identification and Mapping Procedure.

All subjects will undergo the appropriate surgical procedure according to the surgeons and/or hospitals standard practice for breast cancer surgery. The surgical procedures will include either a lumpectomy or a mastectomy.

All subjects will receive the hospital/institutions and surgeons standard pre-operative and post-operative care with the addition of any study specific requirements.

All subjects will have total blood loss recorded at the completion time of surgery as per standard of care.

Either during or immediately post-operatively, the details of the SLNB procedure and surgical procedure will be documented. LN mapping data will be collected including the ability to visualize lymphatic vessels and identify LNs as well as data to confirm the safety of intradermal injection of IC2000. In subjects in whom lymphatic flow through the lymphatic vessels may be occluded or damaged proceed to alternate route of administration of IC2000 and map with SPY.

Failed mapping is defined as no LNs detected by either Tc99m and Gamma Probe, IC2000 and SPY or LNs deemed clinically suspicious.

LNs identified during the mapping procedure will be classified according to Section 7.4, Classification of LNs, and recorded in the CRFs.

[redacted]

12.3.2 Imaging Agent Dosing and Administration of IC2000

The IC2000 solution will be prepared and administered by the appropriate qualified study investigator or operating room personnel. The breast(s) will be injected with IC2000 at the start of surgery.

[redacted]

See Section 7.3.1.1, Injection Technique, for specifics.

12.3.3 Visualization of Lymphatic Vessels and Identification of LNs during Lymphatic Mapping

IC2000 and SPY-PHI (Fluorescent Only) identification criteria:

- LNs identified with NIR fluorescence signal using IC2000 and SPY-PHI *in-vivo*, not confirmed as "hot" *ex-vivo* with Tc-99m and Gamma Probe.

IC2000/SPY PHI and Tc-99m radioactive colloid with gamma probe identification criteria (Both):

- LNs identified with NIR fluorescence signal using IC2000 and SPY-PHI *in-vivo* and confirmed with Tc-99m and Gamma Probe as "hot" utilizing the 10 second count, *ex-vivo* (LN must be 10% or more of the "hottest" node).

Tc-99m radioactive colloid with Gamma Probe identification criteria (Tc99m only):

- LNs identified *in-vivo* with Tc-99m and Gamma Probe as "hot" LNs, with no NIR fluorescence signal using IC2000 and SPY-PHI (LN must be 10% or more of the "hottest" node).
- LNs identified *in-vivo* by Tc-99m/Gamma Probe only, which upon re-assessment with IC2000/SPY are determined to be fluorescent, will be classified by the investigator as "Tc-99m only" LNs (LN must be 10% or more of the "hottest" node).

Clinically suspicious identification criteria (Fluorescent and Tc99 negative):

- Clinically suspicious LNs designated as palpable masses will be excised regardless of visible fluorescence or if deemed 'hot' with a Gamma Probe.

All LNs identified by IC2000/SPY-PHI and Tc-99m/Gamma Probe will be classified *ex-vivo* or *in-vivo* by the investigator:

1. Fluorescent only
2. Tc99m only
3. Both (Fluorescent and Tc99m positive)
4. Clinically suspicious (Fluorescent and Tc99 negative)

[redacted]

12.4 Post-operative Follow-up Visits (Day of discharge to Day 30)

Subjects will have standard of care assessments throughout the study according to the hospital/institution's standard procedures as well as study specific visits on the date of

discharge and Day 30 (±7 days). Day 30 visit will be a telephone call and subjects will be assessed for the following throughout the study:

- Concomitant medications and procedures as described in Section 10.4, Concomitant Medication.
- Adverse events and adverse device effects according to Section 13.1, Evaluation, Recording and Reporting of Adverse Events.

[redacted]

12.5 Histopathology of Excised LN

The presence of lymphoid tissue for each excised LN will be confirmed by tissue analysis. All LNs will be routinely sectioned and stained with [redacted] for pathology assessment as per the hospital/institutions standard procedure.

12.6 Image Acquisition and Transmission

[redacted]

13. 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 injection of Tc-99m should be recorded in the source documents and will be considered part of the subject's medical history.
- All adverse events occurring during the study will be recorded as adverse events on the adverse event CRF.
- Events occurring as a result of the surgery will be reported as adverse events related to the surgical procedure in the adverse event CRF.
- Events related to SPY-PHI will be recorded as adverse device effects in the adverse event CRF.

- Events that are not related to SPY-PHI shall be recorded as adverse events.

- Events related to SPY-PHI that affect a user of the device (non-subject) are recorded as technical complaints.
- Events related to IC2000 and/or Tc99m will be recorded as adverse events related to IC2000 and/or Tc99m in the adverse event CRF.

[redacted]

AEs reported on the CRF will include the date of onset, severity, relationship to SPY-PHI, IC2000 and/or Tc99m, 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.

AEs will be coded using MedDRA and graded according to the National Institutes of Health and National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), v5.0: November 27, 2017 (see Appendix 1).

13.1 Definitions

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

13.2 Adverse Event Descriptions

[redacted]ntensity

The intensity of AEs, including ADEs will be characterized as mild, moderate, severe, life-threatening or fatal as follows:

Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate	Minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living.
Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
Life-threatening	Life-threatening consequences; urgent intervention indicated.

Death	Death related to AE.

Relationship

[redacted]

13.3 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 [redacted] contact listed below:

[redacted]

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 be responsible for reporting SAEs/UADEs to the FDA or Health Canada in accordance with federal regulatory requirements.

The Sponsor will provide documentation of reportable events to the Investigator.

[redacted]

13.4 Follow-up for Adverse Device Effects and Adverse Events

Throughout the study until 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 Day 30 visit. All AEs related to IC2000, SPY-PHI, Tc99m or the mapping 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 if they are related to the study procedures at the discretion of the Investigator.

13.5 Reporting of Technical Complaints / Device Deficiencies

[redacted]

13.6 ADEs Technical Complaints / Device Deficiencies that are UADEs

[redacted]

14. STATISTICAL CONSIDERATIONS

14.1 Analysis PopulationsPer-protocol (PP)

Since this is a non-inferiority design, the PP analysis population will be primary; it will comprise all subjects that: (1) meet all eligibility criteria; (2) received the full dose of tracer / dye; (3) successfully completed the mapping procedure (i.e. have at least one lymph nodes detected *in-vivo* by IC2000 and SPY or by Tc99m and Gamma Probe, or have lymph nodes deemed clinically suspicious), and; (4) have histology confirmed lymph nodes.

[redacted]

Modified Intent to treat (mITT)

The mITT analysis population will comprise all enrolled subjects who received at least one injection of IC2000 and Tc99. All subjects meeting this criterion will be included in the mITT population regardless of whether or not (1) they received lymphatic mapping (i.e. they only had LNs identified through palpation), or (2) received the full dose of tracer / dye. Subjects who have the mapping procedure aborted due to circumstances, such as a higher stage cancer than initially expected, subjects with failed mapping, or subjects without histology confirmed lymph nodes will not be included in the mITT. The mITT population will be used for a secondary analysis of the primary endpoint.

[redacted]

Safety

The safety analysis population will comprise all subjects enrolled in the study who received at least one injection of IC2000 regardless of whether LN mapping was initiated or was successful. All safety endpoints, including the summary of AEs or ADEs in the trial, will be analyzed using this analysis population.

14.2 Demographic and Baseline Characteristics

The demographic and baseline characteristics will be described for the mITT and PP populations with summary statistics including the mean, standard deviation, median, minimum and maximum for continuous variables, and counts and percentages for categorical variables.

The following parameters will be summarized: age, race, body mass index, cancer stage and grade, vital signs, surgical predictive factors, and medical history.

14.3 Primary Objective

To assess the effectiveness of IC2000/SPY during lymphatic mapping and sentinel lymph node biopsy, the proportion of excised lymph nodes identified by IC2000/SPY *in-vivo* and confirmed by histology ($\mathbf{Q_T}$) will be compared with the proportion of excised lymph nodes identified with Tc99m/Gamma and confirmed by histology ($\mathbf{Q_C}$). The denominator for both $\mathbf{Q_T}$ and $\mathbf{Q_C}$ will be the total number of lymph nodes identified and excised that were confirmed by histology, inclusive of clinically suspicious lymph nodes.

The following hypothesis will be tested at the lymph node level:

H0: $\mathbf{Q_T} \leq \mathbf{Q_C} - 0.05$ H1: $\mathbf{Q_T} > \mathbf{Q_C} - 0.05$

To test this hypothesis, the difference $\mathbf{Q_T} - \mathbf{Q_C}$ will be calculated and the associated two-sided 95% confidence interval. If the lower bound of the interval is greater than -0.05, non-inferiority (using the PP population) will be claimed.

[redacted]

14.4 Secondary Objectives

To evaluate the effectiveness of IC2000/SPY and Tc99m/Gamma Probe in the identification of at least one lymph node (histology confirmed lymph node) per subject, the proportion of subjects with at least one lymph node identified with IC2000/SPY *in-vivo* and confirmed by histology ($\mathbf{Q_T}$) and the proportion of subjects with at least 1 lymph node identified with Tc99m/Gamma Probe and confirmed as lymphoid tissue ($\mathbf{Q_C}$) will be described using summary statistics. The denominator for both $\mathbf{Q_T}$ and $\mathbf{Q_C}$ will be the number of subjects where mapping was attempted.

In a secondary analysis, the mITT population will be used instead of the PP population.

To evaluate the effectiveness of IC2000/SPY as an intraoperative fluorescence visualization tool in delineation and mapping of lymphatic vessels in the identification of lymph nodes (histology confirmed lymph nodes), the proportion of lymph nodes identified by IC2000/SPY (histology confirmed lymph nodes) by following a fluorescent lymphatic vessel and the proportion of lymph nodes identified by IC2000 and SPY (histology confirmed lymph nodes) with no lymphatic vessels visible by IC2000/SPY will be described using summary statistics. Denominator will be the total number of lymph nodes

identified by any method (histology confirmed). The concordance rate and the findings of discordant lymph nodes will also be presented.

14.5 Other Analyses

[redacted]

14.6 Safety Objective

Safety variables will be documented and summarized for all subjects in the safety analysis population. Safety variables will include all AEs and ADEs, concomitant medications, vital signs and blood loss assessments.

AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) and coded using MedDRA. AEs and ADEs occurring during the study will be summarized descriptively with the total number of AEs and ADEs as well as the number and percentage of subjects experiencing AEs and ADEs, overall and by system organ class and preferred term.

Associated AEs that investigators suspect are related to study treatment will also be summarized. Summary of each type of event will be prepared by severity and for all severities combined.

14.7 Handling of Missing Data

[redacted]

14.8 Sample Size Considerations

This is a single arm, non-inferior, sequential design, paired comparison study of IC2000 and SPY with the standard of care, Tc99m/Gamma Probe in the identification of lymph nodes during lymphatic mapping and sentinel lymph node biopsy. The sample size calculation for the primary endpoint was performed using nQuery Advisor® 7.0 (Copyright© 1995-2007, Statistical Solutions Ltd). To support the sample size calculation, the average LN detection rate with IC2000 and SPY (Q_T) of 96% was assumed, based on the recent meta-analyses; Mok et al.[56] An average detection rate of 91.6% has been assumed for Tc99m and Gamma Probe (Q_C)[57] A 5% non-inferiority margin is deemed to be conservative for sentinel lymph node biopsy (SLNB).

Assuming an average of 2 excised LNs per patient evaluated by both methodologies with 11.2% discordance [57], 137 subjects would be required to prove the non-inferiority of IC2000 and SPY with a non-inferiority margin of 5% using a one-sided 2.5% alpha and 90% power. A 1.0% Q_T advantage would establish non-inferiority.

Lower one-sided 97.5% confidence bound: Difference in paired proportions (simulation)

	90% Power	1-sided p=0.025
Confidence level, 1-α (one-sided)	0.975	0.975
Expected difference, $Q_T - Q_C$, Δ	0.044	0.01
Proportion discordant, $d = q_{10} + q_{01}$	0.112	0.112
Proportion both yes, q_{11}	0.883	0.883
Lower limit for $Q_T - Q_C$, LL	-0.050	-0.050
Number of simulations	1000	1000
Random seed for simulations	123	123
Power (%)	90	NA
n (number of paired evaluations)	137	137

Based on a 2-level hierarchical model in which nodes are nested within subjects, and given that we expect an average of 2 nodes to be excised per patient[21] the aforementioned sample size needs to be multiplied by an inflation factor (IF), aka Design Effect (DEFF[54, 55]), of 1+(n-1)*ICC where n is the average sample size per cluster and ICC (expected to be at most 0.1) is the intra-class correlation: IF = 1+ (2x2 – 1) x 0.1 = 1.3, where n was multiplied by 2 due to the fact that LNs will be identified using 2 different methods. Based on a total of 274 LNs and an IF of 1.3, a sample size of 356 lymph nodes will be required. Estimating that 6% of patients will be excluded from the per-protocol (PP) population (see Section 14.1), approximately 379 LNs are required.

15. ESTIMATED DURATION OF THE STUDY

[redacted]

16. STUDY ETHICAL CONSIDERATIONS

16.1 Ethical Conduct of the Study

The study will be conducted in accordance with US 21 CFR Parts 50, 54, 56, 312 and 812 as well as ICH E6: Good Clinical Practice: Consolidated Guideline. It will be constituted in keeping with the principles of ICH E8: General Considerations for Clinical Trials and Part C, Division 5 of the Canadian Food and Drug Regulations. Any additional requirements imposed by the local Institutional Review Board / Ethics Committee / Research Ethics Board or regulatory agency will be followed as necessary.

16.2 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.

16.3 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.

16.4 Data and Safety Monitoring Board

The study will be reviewed on an as needed basis by an independent Data and Safety Monitoring Board (DSMB). The statistician will prepare a report for the DSMB in advance of the scheduled review meeting using the report template provided by the DSMB. A DSMB charter will outline specific safety and data monitoring procedures.

17. ADMINISTRATIVE PROCEDURES

17.1 Sponsor's Responsibilities

17.1.1 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

[redacted]

during the Study

[redacted]

[redacted]

17.4 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.

17.5 Records Retention

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

17.6 Investigator's Responsibilities

17.6.1 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 16.3, Institutional Review Board, Ethics Committee, or Research Ethics Board (IRB).

17.6.2 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:

[redacted]

17.6.3 Study Devices and Imaging Agents

The Investigator is responsible for ensuring the SPY-PHI Systems, including IC2000, are controlled and are used or dispensed only to subjects enrolled in the study. Only Investigators identified on the Signature and Delegation Log may use SPY-PHI for the purposes of this study.

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

The Investigator will ensure that the SPY-PHI System is returned, if they are provided by NOVADAQ for this study, 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.

17.6.4 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.

18. DATA MANAGEMENT

[redacted]

[redacted]

19. POLICY FOR PUBLICATION AND PRESENTATION OF DATA

[redacted]

[redacted]

[redacted]

nodes in breast cancer patients. Breast Cancer Res. Treat. 127, 163–170 (2011).

[redacted]

[redacted]

experience. Breast cancer research and treatment. 143, 333–42 (2014).

[redacted]

[redacted]

[redacted]