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Official Title: A Post-market Feasibility Study Evaluating Location Accuracy Using the superDimension™ Navigation System Version 7.2 With Fluoroscopic Navigation Technology in Subjects Undergoing Lung Lesion Biopsy

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Clinical Investigation Plan

Clinical Investigation Plan/Study Title	A post-market feasibility study evaluating location accuracy using the superDimension™ Navigation System Version 7.2 with Fluoroscopic Navigation Technology in subjects undergoing lung lesion biopsy
Clinical Investigation Plan Identifier	MDT18004ILSFNV
Study Product Name	superDimension™ Navigation System Version 7.2 with Fluoroscopic Navigation Technology
Sponsor/Local Sponsor	Medtronic Lung Health Minimally Invasive Therapies Group 161 Cheshire Lane, Suite 100 Plymouth, MN 55441
Document Version	Final Version 1.0, 09-APR-2018
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[redacted]	
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1. Investigator Statement

Study product Name	superDimension™ Navigation System Version 7.2 with Fluoroscopic Navigation Technology
Sponsor	Medtronic Lung Health Minimally Invasive Therapies Group 161 Cheshire Lane, Suite 100 Plymouth, MN 55441
Clinical Investigation Plan Identifier	MDT18004ILSFNV
Version Number/Date	Final Version 1.0, 09-APR-2018
I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to comply with ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice) and the International Conference on Harmonisation (ICH) of Technical Requirements For Registration of Pharmaceuticals For Human Use, ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 (R1). I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.	
Principal Investigator's Signature:	
Principal Investigator's Name:	
Institution:	
Date:	

Table of Contents

2. Glossary

2.1. Terms

Acronym / Term	Definition
AE	adverse event
AP	anteroposterior
CBCT	cone-beam computed tomography
CIP	clinical investigation plan
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ENB	electromagnetic navigation bronchoscopy
eCRF	electronic case report form
EWC	extended working channel
FDA	Food and Drug Administration
GCP	good clinical practice
ICF	informed consent form
ICH	International Conference on Harmonisation
IFU	instructions for use
ILS	Medtronic Interventional Lung Solutions
IRB	institutional review board
LG	locatable guide
MDR	medical device reporting
ROSE	rapid on-site evaluation
SAE	serious adverse event
SAP	statistical analysis plan

2.2. Definitions

Adequate Periprocedural Location

The location of the extended working channel when the proceduralist makes the decision that placement is adequate and clinically acceptable to proceed with tissue sampling based on location confirmation by cone-beam computed tomography (CBCT).

Adverse Event

Please refer to Section 11.1.1.

Bronchopulmonary Hemorrhage

A disorder characterized by bleeding from the bronchial wall and/or lung parenchyma. Degree of severity will be classified according to Common Terminology Criteria for Adverse Events (CTCAE) grade as follows (a semicolon indicates "or" within the description of the grade):

- Grade 1: Mild symptoms; intervention not indicated
- Grade 2: Moderate symptoms; medical intervention indicated
- Grade 3: Transfusion, invasive intervention indicated (e.g., hemostasis of bleeding site)
- Grade 4: Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
- Grade 5: Death

Common Terminology Criteria for Adverse Events

A set of criteria for the standardized classification of adverse effects of drugs used in cancer therapy. The CTCAE system is a product of the US National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP).[1] This protocol will use Version 5.0, available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

ENB Procedure Time

Total time from the first entry of the extended working channel or locatable guide until the last exit of the extended working channel.

Device Deficiency

See Section 11.1.6.

Investigational Medical Device

For the purpose of this clinical investigation plan, an Investigational Medical Device is defined as, "a device, including a transitional device, which is the object of an investigation." The Investigational Medical Device being evaluated in this study is the superDimension™ Navigation System Version 7.2 with Fluoroscopic Navigation Technology, which has been cleared by the FDA.

Lesion Size

Defined as greatest diameter of target lesion.

Navigation Success

The proportion of cases in which the operator is able to successfully navigate to the lung target with ENB guidance and obtain tissue for biopsy.

Pneumothorax

A disorder characterized by abnormal presence of air in the pleural cavity resulting in the collapse of the lung. Degree of severity will be classified according to CTCAE grade as follows (a semicolon indicates "or" within the description of the grade):

- Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Symptomatic; intervention indicated (e.g., tube placement without sclerosis)
- Grade 3: Sclerosis and/or operative intervention indicated; hospitalization indicated
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death

Relational Accuracy

Describes the 3-dimensional relationship between the catheter and the lesion in terms of distance, vector, and trajectory.

Respiratory Failure

A disorder characterized by impaired gas exchange by the respiratory system resulting in hypoxia and a decrease in oxygenation of the tissues that may be associated with an increase in arterial levels of carbon dioxide. Degree of severity will be classified according to CTCAE grade as follows (a semicolon indicates "or" within the description of the grade):

- Grade 4: Life-threatening consequences; urgent intervention, intubation, or ventilatory support indicated
- Grade 5: Death

Serious Adverse Event

Please refer to Section 11.1.2.

Technical Success

Successful completion of Local Registration utilizing Fluoroscopic Navigation Technology in superDimension™ Navigation System Version 7.2.

Total Procedure Time

Total time from the first entry of the bronchoscope to the last exit of the bronchoscope.

3. Synopsis

Title	A post-market feasibility study evaluating location accuracy using the superDimension™ Navigation System Version 7.2 with Fluoroscopic Navigation Technology in subjects undergoing lung lesion biopsy
Clinical Study Type	Post-Market Feasibility
Product Name	superDimension™ Navigation System Version 7.2 with Fluoroscopic Navigation Technology
Sponsor	Medtronic Lung Health Minimally Invasive Therapies Group 161 Cheshire Lane, Suite 100 Plymouth, MN 55441
Investigation Purpose	The purpose of this investigation is to confirm the clinical accuracy of the superDimension™ Navigation System Version 7.2 with Fluoroscopic Navigation Technology.
Product Status	superDimension™ Navigation System Version 7.2 is cleared by FDA
Primary Objective	The primary objective of this post-market feasibility study is to confirm the location accuracy of the local registration feature of the superDimension™ Navigation System Version 7.2 in subjects undergoing lung lesion biopsy.
Primary Endpoint	The Primary Endpoint is the measured ability of the superDimension™ Navigation System v7.2 with Fluoroscopic Navigation Technology to place the center of the virtual navigation target (green ball) on the intended target lesion as confirmed by cone-beam computed tomography (CBCT). The primary endpoint will be evaluated in Technically Successful cases (local registration complete).
Secondary Objectives	The following secondary endpoints will be evaluated in all enrolled subjects: • Number of cases that are technically successful (successful completion of local registration) • In cases that are not technically successful, reason for

	incomplete local registration in each target lesion • Investigator confirmation that the catheter is in an "Adequate Periprocedural Location" (the location of the extended working channel with the proceduralist makes the decision that placement is adequate and clinically acceptable to proceed with tissue sampling based on location confirmation by CBCT) • Total procedure time • ENB procedure time • Total fluoroscopy time, as measured by the fluoroscopy system • Adequacy of the ENB-aided tissue sample for rapid on-site evaluation (ROSE) of cytologic samples by pathology (when applicable) • Histopathological call based on ROSE of the ENB-aided tissue sample (when applicable) • Final pathology results of the ENB-aided tissue sample • Biopsy tools used, tool order, number of passes, and diagnoses for each tool based on ROSE and final pathology of the ENB-aided sample In Technically Successful cases (local registration complete): • Percentage of cases in which the *intended* lesion is correctly identified (as opposed to a non-target lesion or normal lung tissue) as indicated by the system software. • Relational Accuracy in cases in which the *Intended* lesion is targeted.

Safety Assessments	The following safety endpoints will be evaluated in all enrolled subjects. These events will be evaluated for their relationship to the study device and study procedure, and classified according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5. • Incidence of all pneumothorax related to ENB index procedure • Incidence of CTCAE Grade ≥2 pneumothorax related to the ENB index procedure • Incidence of all bronchopulmonary hemorrhage related to ENB index procedure • Incidence of CTCAE Grade ≥2 bronchopulmonary hemorrhage related to the ENB index procedure • Incidence of CTCAE Grade≥4 respiratory failure related to ENB index procedure In addition to the Safety Endpoints described above, all Adverse Events related to the superDimension™ navigation system, associated tools, or ENB procedure will be collected. Adverse events and safety endpoints will be collected immediately post-procedure and at 7 days post procedure.
Study Design	This post-market feasibility study will include subjects who meet the criteria specified below. Assessments will occur at baseline, during and immediately after the procedure, and at 7 days post procedure by telephone.
Randomization	Not Applicable
Clinical Sites	Up to 5 clinical sites in the United States are planned
Sample Size	This study will enroll up to 50 subjects meeting the inclusion criteria, with a maximum of 25 subjects per site. A maximum of five roll-in cases will be allowed per investigator, as described in Section 8.2.1.

Inclusion/Exclusion Criteria	Inclusion Criteria 1. Subject presents with lung lesion(s) greater than 10 mm in diameter amenable to evaluation by ENB at the time of evaluation 2. Lesion is intended to be biopsied by the participating investigator 3. Subject is willing and able to provide informed consent to participate in the study 4. Subject is a candidate for an elective ENB procedure 5. Subject is over the age of 18 Exclusion Criteria 1. Central lesions that are not visible endobronchially or could be reached by a flexible bronchoscope or endobronchial ultrasound (EBUS) without the utilization of ENB 2. Lesions within 10 mm of the diaphragm 3. The subject is unable or unwilling to comply with study follow-up schedule 4. The subject has participated in an investigational drug or device research study within 30 days of enrollment that would interfere with this study 5. Female subjects who are pregnant or nursing as determined by standard site practices
Study Procedures and Assessments	Enrolled subjects will first undergo a standard ENB procedure to navigate to within 2.5 cm of the target lesion. Local registration with Fluoroscopic Navigation Technology will be conducted and fluoroscopy and CBCT scans will be used to document that the biopsy tool is correctly positioned in the target lesion in three dimensions. Efficacy endpoints will be collected during the procedure and safety will be evaluated through 7-day follow-up, as described above.
Statistics	No formal statistical comparisons or sample size calculations will be made for this post-market feasibility study. **Interim Analysis**: Will be conducted after roll-in procedures have been completed for the purpose of evaluating workflow and data

	validity. **Final Analysis**: Will be conducted after all subjects have completed the procedure and the 7-day follow-up for the purpose of evaluating the primary and secondary endpoints.

4. Introduction

4.1. Background

Electromagnetic navigation bronchoscopy (ENB) using the superDimension™ navigation system is an image-guided approach that uses three-dimensional reconstructed computed tomography (CT) scans and sensor location technology to guide endoscopic tools to lung lesions.[2] To date, over thirty clinical studies with data from over 2,100 subjects have been published describing outcomes of ENB-aided biopsy of peripheral lung lesions using the superDimension™ navigation system. ENB-aided diagnostic yield ranges from 39% to 97%.[3-34] Pneumothorax is the most common complication, occurring in approximately 3% of patients in a recent meta-analysis,[35] lower than the pooled 20% rate reported for transthoracic needle biopsy.[36] The prospective, multicenter NAVIGATE study evaluated ENB using the superDimension™ navigation system v7.0 and v6.0. Pneumothorax CTCAE Grade ≥2 occurred in 3.2% of subjects. Any-grade pneumothorax occurred in 4.9% of subjects. Bronchopulmonary hemorrhage was 1.0% CTCAE Grade ≥2 and 2.3% overall. CTCAE Grade ≥4 respiratory failure occurred in 0.6% of subjects. There were no deaths related to the ENB device or associated tools.[37]

Despite the volume of safety and efficacy data on the superDimension™ navigation system, one remaining challenge is that the reconstructed images are based on pre-procedure CT scans of the patient without real-time confirmation of catheter location relative to the target lesion. In addition, CT-to-body divergence can occur when the patient's anatomy does not perfectly align with the three-dimensional CT. Because the inhale level during the CT scan is different than during the procedure, the volume and shape of the lung are different. Other factors resulting in deformation or divergence from the original CT may include the presence and push by the bronchoscope or catheter, the reaction of airway muscles to sedation or anesthesia, a different patient position, bed curvature, and anatomical changes.

While real-time fluoroscopy is frequently used during ENB to circumvent these challenges, small lesions or those obscured by dense tissue, blood vessels, or bone may not be clearly visible under two-dimensional fluoroscopy.[38] Anatomy can also be blurred together rather than clearly separated. In the NAVIGATE study, at least 40% of lung lesions were not visible on fluoroscopy.[37]

The superDimension™ navigation system version 7.2 is a modification of the version 7.1 system. Version 7.2 (v7.2) adds fluoroscopic navigation technology with enhanced three-dimensional fluoroscopy to improve the physician's ability to biopsy lung lesions by rotating the fluoroscope laterally around the lesions. The fluoroscopic navigation technology allows for optional local registration that updates the catheter position relative to the target using fluoroscopic images with ENB to compensate for CT-to-body divergence during the procedure. The local registration process focuses on a small region of

interest around the target and refines the three-dimensional model based on the fluoroscopic image data. This takes into consideration any changes in the patient's positioning or other changes compared to the CT scan. Because the data is taken at the time of the procedure and covers a specific region of the lung, the system can create a more precise model around the target thus minimizing local CT-to-body divergence.

The current feasibility study will evaluate the location accuracy of the superDimension™ Navigation System v7.2 with Fluoroscopic Navigation Technology to determine if the local registration feature allows accurate lesion targeting, with the same safety profile observed for previous superDimension navigation system versions.

4.2. Purpose

The purpose of this investigation is to confirm the clinical accuracy of the superDimension™ Navigation System v7.2 with Fluoroscopic Navigation Technology.

5. Objectives and Endpoints

5.1. Primary Objective

The primary objective of this post-market feasibility study is to confirm the location accuracy of the local registration feature of the superDimension™ navigation system v7.2 in subjects undergoing lung lesion biopsy.

5.2. Primary Endpoint

The Primary Endpoint is the measured ability of the superDimension™ Navigation System v7.2 with Fluoroscopic Navigation Technology to place the center of the virtual navigation target (green ball) on the intended target lesion as confirmed by CBCT.

The primary endpoint will be evaluated in Technically Successful cases (local registration complete).

[redacted]

5.3. Secondary Endpoints

The following secondary endpoints will be evaluated in all enrolled subjects:

- Number of cases that are technically successful (successful completion of local registration)
- In cases that are not technically successful, reason for incomplete local registration in each target lesion
- Investigator confirmation that the catheter is in an "Adequate Periprocedural Location" (the location of the extended working channel with the proceduralist makes the decision that placement is adequate and clinically acceptable to proceed with tissue sampling based on location confirmation by CBCT).
- Total procedure time
- ENB procedure time
- Total fluoroscopy time, as measured by the fluoroscopy system
- Adequacy of the ENB-aided tissue sample for rapid on-site evaluation (ROSE) of cytologic samples by pathology (when applicable)
- Histopathological call based on ROSE of the ENB-aided tissue sample (when applicable)
- Final pathology results of the ENB-aided tissue sample
- Biopsy tools used, tool order, number of passes, and diagnoses for each tool based on ROSE and final pathology of the ENB-aided sample

In Technically Successful cases (local registration complete):

- Percentage of cases in which the *intended* lesion is correctly identified (as opposed to a non-target lesion or normal lung tissue) as indicated by the system software.
- Relational Accuracy in cases in which the *Intended* lesion is targeted.

5.4. Safety Endpoints

The following safety endpoints will be evaluated in all enrolled subjects. These events will be evaluated for their relationship to the study device and study procedure, and classified according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Adverse events and safety endpoints will be collected immediately post-procedure and at 7 days post procedure.

- Incidence of all pneumothorax related to ENB index procedure
- Incidence of CTCAE Grade ≥2 pneumothorax related to the ENB index procedure
- Incidence of all bronchopulmonary hemorrhage related to ENB index procedure
- Incidence of CTCAE Grade ≥2 bronchopulmonary hemorrhage related to the ENB index

procedure

- Incidence of CTCAE Grade ≥4 respiratory failure related to ENB index procedure

In addition to the Safety Endpoints described above, all Adverse Events related to the superDimension™ navigation system, associated tools, or ENB procedure will be collected as described in Section 11.

6. Study Design

This post-market feasibility study is planned in up to 50 subjects meeting the inclusion criteria and undergoing elective ENB with the superDimension™ Navigation System v7.2 with Fluoroscopic Navigation Technology. The study will confirm the location accuracy of the optional local registration feature. Enrolled subjects will first undergo a standard ENB procedure to navigate to within 2.5 cm of the target lesion. Local registration with Fluoroscopic Navigation Technology will be conducted and fluoroscopy and CBCT scans will be used to document that the biopsy tool is correctly positioned in the target lesion in three dimensions. Details of the procedure are included in Section 9.7.3. Periprocedural endpoints will include confirmation of accurate positioning within the target lesion, technical success, relational accuracy, adequate periprocedural location, procedure time, adequacy of tissue capture for pathology, tool usage, and histopathological results, as described below. Safety will be evaluated immediately post-procedure and at 7 days post-procedure.

6.1. Duration

Assessments will occur at baseline, during the procedure, immediately post-procedure, and 7 days post procedure by telephone.

Based on the expected enrollment rate of 5 subjects per site per month, the total duration of the study from first subject enrollment to last subject follow-up is expected to be approximately 6-8 months.

6.2. Rationale

The purpose of this investigation is to confirm the clinical accuracy of the superDimension™ Navigation System v7.2 with Fluoroscopic Navigation Technology.

Several aspects of the study design make it desirable compared to other options. The v7.2 software includes an optional local registration feature intended to compensate for CT-to-body divergence though incorporation of additional fluoroscopic imaging data taken during the electromagnetic navigation procedure. The primary objective of this post-market feasibility study is to confirm the location accuracy of the local registration feature of the superDimension™ navigation system v7.2 in subjects undergoing lung lesion biopsy. This objective focuses on the intended use of the system at an immediate periprocedure timepoint, reducing the burden on subjects.

Enrollment of eligible subjects with minimal inclusion and exclusion criteria will ensure a more representative and generalizable sample. The targeted number of 50 subjects (25 per site) was chosen as the minimal number required to evaluate the technology at each site and is consistent with first experience studies evaluating the ENB technology.[3-5, 7]

Design verification and validation test results provide reasonable assurance that the device conforms to the requirements for its indications for use and intended use. A thorough risk assessment has shown that the addition of the local registration feature does not significantly change the device risks. Design verification performed on the superDimension™ navigation system v7.2 confirmed that the superDimension™ navigation system met its product specification and system requirements. Regression testing was executed to verify the modifications did not impact unmodified software elements. Design validation was successfully performed under simulated use conditions by representative users from targeted user groups including qualified bronchoscopists and clinicians. Each user group performed typical use scenarios defined in the design validation protocol. In conclusion, the design validation study ensured that the superDimension™ navigation system v7.2 conformed to defined user needs and intended uses.

Bench testing for the superDimension™ navigation system v7.2 consisted of verification of software and hardware elements of the product to confirm that the device performs as intended. Formal execution of software test cases, including regression testing, was completed in two test cycles to verify that the software meets the designated requirements. Hardware verification testing was performed on the only new hardware component of the system, the fiducial marker board, to demonstrate the component meets all design requirements. Overall, the results of the bench testing, including all related risk activities, showed that the superDimension™ navigation system v7.2 meets the design requirements for all hardware and software components and performs as intended.

Prior clinical studies of the superDimension™ navigation system are described in Section 4.1.

The current study will evaluate the location accuracy superDimension™ Navigation System v7.2 to determine if the local registration feature allows more accurate lesion targeting, with the same safety profile observed for previous superDimension™ navigation system versions.

7. Product Description

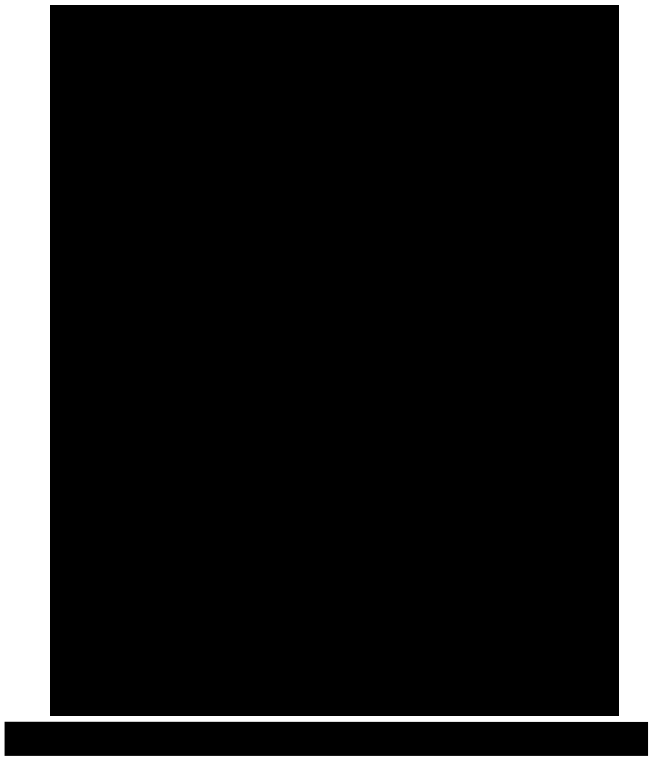
7.1. General

superDimension™ navigation system v7.2 is a device that guides endoscopic tools to a target in or adjacent to the bronchial tree on a path identified by a previous CT scan. The superDimension™ navigation system v7.2 allows visualization of the target and the interior of the bronchial tree; placement of catheters in the bronchial tree; and placement of radiosurgical and dye markers into soft lung tissue to guide radiosurgery and thoracic surgery.

The v7.2 software includes an optional local registration feature intended to compensate for CT-to-body divergence. Incorporation of additional fluoroscopic imaging data taken during the electromagnetic navigation procedure allows for 3D reconstruction of a small region of interest in the lung to compensate for possible CT-to-body divergence. Local registration is an optional feature and can be used at the physician's discretion.

The superDimension™ navigation system v7.2 includes a Procedure application software modification and one additional stand-alone hardware component, called a fiducial marker board. The local registration feature uses a fluoroscopic video taken during the procedure and a fiducial marker board to allow 3D reconstruction of a small region of interest.

Reconstructing three-dimensional data from the multiple fluoroscopic 2D images requires knowing the position of the fluoroscope for every image relative to a fixed coordinate system. The fluoroscope projection angle is measured by detecting (through image processing) a grid of non-ferromagnetic spheres incorporated into the fiducial marker board [redacted].



This grid of spheres, which is clearly visible under fluoroscopy, is used to determine the fluoroscope (camera) position and angle for each fluoroscopic video frame. The grid structure is laid out as a regular grid (15 mm separation in 2 dimensions) and treated as infinite in the fluoroscope plane. This means that the algorithm can use any visible portion of the grid to determine the angle. The grid is attached to the existing location board in a way that aligns the ENB coordinate system. The location board is part of

the localization system that is placed underneath the patient bed mattress. Solving for the fluoroscope position and angle relative to the grid, provides the exact orientation for the fluoroscope in the ENB antenna coordinates. This enables the system to create a 3D reconstruction aligned with the ENB coordinate system. Therefore, the ENB catheter position relative to the target in the ENB coordinates system is known and adjusted in the ENB coordinate system accordingly.

7.2. Dosage Form and Route of Administration

Not Applicable.

7.3. Manufacturer

The superDimension™ Navigation System v7.2 with Fluoroscopic Navigation Technology is manufactured by Covidien llc, an indirect wholly owned subsidiary of Medtronic plc.

7.4. Packaging

The device includes hardware, Planning and Procedure software, disposable sterile devices, and disposable non-sterile components.

7.5. Intended Population

The superDimension™ Navigation System v7.2 with Fluoroscopic Navigation Technology is indicated for patients when it is necessary to guide an endoscopic tool in the pulmonary tract when the indications for such an examination are present in the patient. Not for pediatric use.

7.6. Equipment

Equipment for the study includes:

- CBCT system, such as the Philips Allura Xper FD20 Fluoroscopy System
- The superDimension™ navigation system v7.2 (Figure 4): Includes a Procedure application software modification and one additional stand-alone hardware component, called a fiducial marker board.

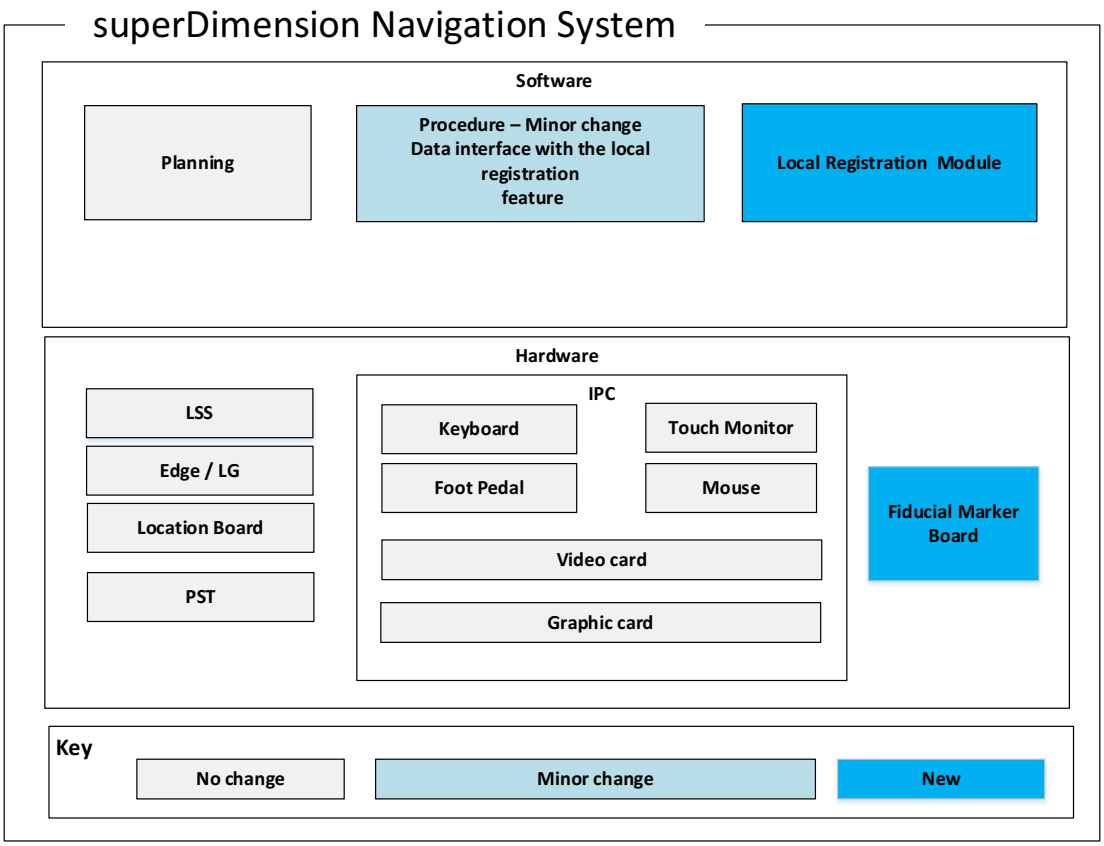


Figure 4. superDimension™ navigation system v7.2 components

7.7. Product Use

The local registration feature requires a fluoroscopic video focused on the region of interest taken at the time of the ENB procedure. The fluoroscopic video is sent to the superDimension™ console through the video input channel. The physician then identifies or marks the tip of the catheter and the target. To facilitate this marking, the module provides visualization of soft tissue in the lung by an image processing mechanism. The image processing reconstructs a 3D volume and enables image slice display throughout that volume. As part of the visualization mechanism, each point in each image is associated with a point in three-dimensional space created from the fluoroscopic video.

Once the three-dimensional location of the catheter and target are established, the local registration feature performs an update of the catheter position in the ENB system. The update is based on the three-dimensional position of the catheter relative to the target obtained from the reconstructed three-dimensional data.

The ENB procedure consists of the following primary procedure steps (Figure 5).

This is a brief explanation of the proposed standard-of-care use and is not the procedure to be used in the current clinical study.

Figure 5: ENB Procedure Steps

A brief explanation of the ENB procedure steps is provided below.

1. **Start Procedure Application**: The physician logs onto the system and selects the procedure button from the home screen.
2. **Setup**: During setup, the physician verifies that the equipment and room are correct as previously qualified. The physician also loads the specific patient plan created in the planning software.
3. **Registration**: During the registration, the locatable guide is placed inside the extended working catheter which is then inserted through the bronchoscope channel. The locatable guide contains a sensor in the tip that reads the magnetic field generated by the localization system. This allows the system to determine the locatable guide's position. During registration, the locatable guide gathers survey data from the patient which is matched with the three-dimensional map generated from the CT scan during planning. When the registration is completed successfully, the physician can begin navigation.
4. **Navigation**: During navigation, the physician uses the images of the patient's lungs displayed in the system views on the computer screen to steer the locatable guide catheter to the predetermined target.
5. **Local Registration**: Once the physician is within 2.5 cm of the target, the local registration feature can be launched. If desired, the physician selects the launch button on the screen to initiate the local registration process. The purpose of local registration is to account for CT-to-body divergence. CT-to-body divergence exists where the patient's anatomy does not perfectly align with the three-dimensional CT. Because the inhale level during the CT scan is different than during the procedure, the lung's volume and shape are different. Other factors resulting in deformation or divergence from the original CT may include the presence and push by the bronchoscope or catheter, airway muscle's reaction to sedation or anesthesia, a different

patient position, bed curvature, and anatomical changes. The software adjusts for this as much as possible during the initial registration procedure in step 3 by using an algorithm to perform a best fit alignment to the entire patient's lungs. Since it is a best fit algorithm, some deviation between the model and actual anatomy can still exist and is called CT-to-body divergence.

6. The local registration process focuses on a small region of interest around the target and refines the three-dimensional model based on the fluoroscopic image data. This takes into consideration any changes in the patient positioning or other changes compared to the CT scan. Because the data is taken at the time of the procedure and covers a specific region of the lung, the system can create a more precise model around the target thus minimizing local CT-to-body divergence.
7. When the local registration feature is selected, the software guides the physician through the following steps:
    a. Setup
    b. Image capture using the fiducial marker board to determine angle
    c. Catheter and target marking
    d. Confirmation of catheter and target marking
    e. Once the physician has confirmed the catheter and target marking, the local registration feature is exited, the catheter position is updated based on the local registration, and the ENB procedure continues exactly as in the predicate by finalizing the navigation to the target. The physician may also choose to disregard the update and revert to the previous (initial) registration or to repeat the local registration feature.
8. **End Procedure**: Once the physician has completed navigation and performed any additional fiducial marker placement or biopsies, the extended working channel is removed and the procedure completed.

7.8. Product Training Requirements

Only a qualified bronchoscopist (i.e., physician) may navigate with the superDimension™ navigation system. A clinician, under the direct supervision of the bronchoscopist, may assist in the navigation system setup and provide care to the patient during the ENB procedure. This may be a hospital or clinic employee that has received system training.

In order to use the local registration feature, a service representative must visit the facility and verify that there is a compatible fluoroscope, attach the fiducial marker board, install software, and ensure that the system performs as intended. Once set up, the module is used during a standard procedure when the locatable guide is within 2.5 cm from the target.

Each investigator participating in the clinical trial and the associated clinical study staff will receive training on the clinical protocol, as well as the ENB procedure utilizing the superDimension™ navigation system v7.2. Physicians must demonstrate proficiency with the superDimension™ navigation system v7.2.

7.9. Product Receipt and Tracking

All products used in this study will be commercially available, and therefore do not require receipt and tracking information to be collected. This does not exclude the collection of Lot and/or Serial Numbers for the purpose of post market vigilance activities.

7.10. Product Storage

All products used will be commercially available, and are expected to be stored per the site's standard practice for medical equipment.

7.11. Product Return

Not applicable, all study equipment to be utilized will be commercially available.

7.12. Product Accountability

Not applicable, all study equipment to be utilized will be commercially available.

7.13. Intended Claims

Claims and intended performance of the study product (including aspirational claims) to be verified by the study:

- Ability to compensate for localization divergence (induced by CT-to-body divergence)
- Ability to locally register and enhance lesion visibility
- Provide enhanced visualization
- Provide updated catheter position relative to the nodule once nodule location is confirmed

8. Selection of Subjects

8.1. Study Population

This study will be conducted in subjects over the age of 18 undergoing elective biopsy of lung lesions greater than 10 mm in diameter. Additional inclusion/exclusion criteria are listed below.

8.2. Subject Enrollment

This study will enroll up to 50 subjects meeting the inclusion criteria, with a maximum of 25 subjects per site. Up to 5 clinical sites in the United States are planned.

Subjects meeting the inclusion/exclusion criteria below will be enrolled. Following signing the informed consent form (ICF), the point of enrollment is defined as the entry of the first locatable guide.

The ENB procedure will be performed per the System User Manual, applicable product instructions for use (IFU) and the institution's standard practice. Subjects will be considered for the study if they meet specified inclusion criteria and none of the exclusion criteria. The criteria for enrollment must be followed explicitly.

8.2.1. Roll-in Subjects

A maximum of five roll-in cases will be allowed per investigator. The purpose of the roll-in cases is to provide consistency in the physician user base within the study and optimize procedural methods. Roll-in subjects will be considered study participants and will complete all protocol-required procedures and exams. An interim analysis will be conducted after the completion of roll-in enrollment to evaluate study workflow and data validity. The protocol will be amended if necessary.

8.3. Inclusion Criteria

1. Subject presents with lung lesion(s) greater than 10 mm in diameter amenable to evaluation by ENB at the time of evaluation
2. Lesion is intended to be biopsied by the participating investigator
3. Subject is willing and able to provide informed consent to participate in the study
4. Subject is a candidate for an elective ENB procedure
5. Subject is over the age of 18

8.4. Exclusion Criteria

1. Central lesions that are not visible endobronchially or could be reached by a flexible bronchoscope or endobronchial ultrasound (EBUS) without the utilization of ENB
2. Lesions within 10 mm of the diaphragm
3. The subject is unable or unwilling to comply with study follow-up schedule
4. The subject has participated in an investigational drug or device research study within 30 days of enrollment that would interfere with this study

5. Female subjects who are pregnant or nursing as determined by standard site practices

9. Study Procedures

Below is a description of the procedures that the subject will undergo during the clinical study.

9.1. Schedule of Events

Variables to be collected, follow-up visit schedule, and tests to be performed at each visit are described in **Table 1** below.

Table 1. Schedule of Events

	Baseline (Day - 30 to Day 0)	**During and immediately post-procedure (Day 0)**	**7 days Post-Procedure (window = 4-7 days)**
Informed consent	X		
Eligibility criteria	X		
Demographics	X		
Medical history	X		
Procedural information		X	
Lesion characteristics	X	X	
Adverse event assessment		X	X
Biopsy results		X	X

9.1.1. Overview of Study Procedures

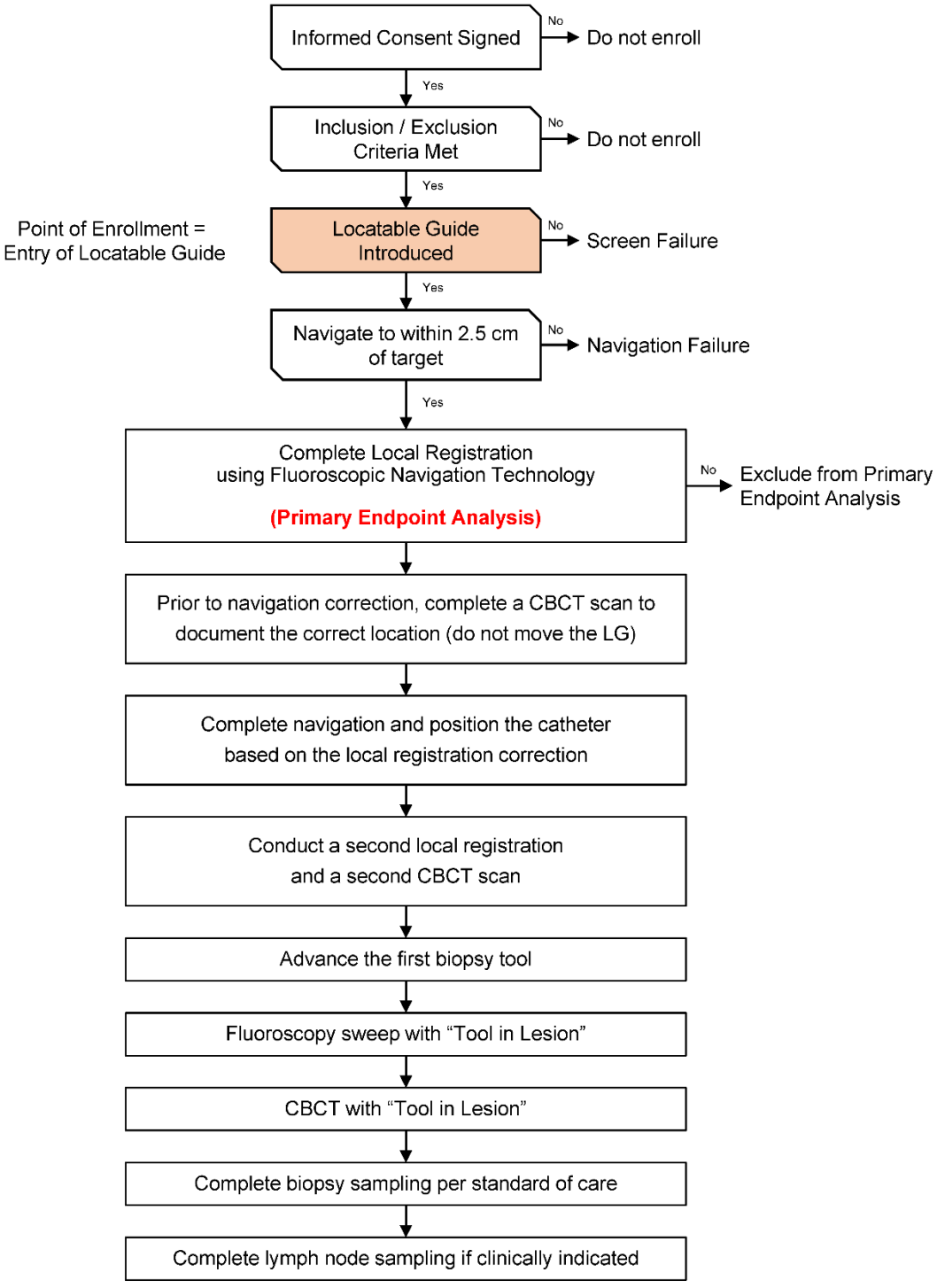


Figure 6. Procedure Steps

9.2. Subject Screening

A baseline visit will be performed within 30 days prior to the scheduled procedure to assess study eligibility. Consented subjects will be considered for the study if they meet specified inclusion criteria and none of the exclusion criteria. The criteria for enrollment must be followed explicitly.

Subjects who provide study consent, but then are determined to be ineligible prior to the ENB procedure will be considered Screen Failures and will not require additional study follow-up visits. The reason for the Screen Failure will be clearly documented on the applicable electronic case report forms (eCRFs). Screen Failures will not be counted towards the number of study subjects.

9.3. Prior and Concomitant Medications

All prior and concomitant medications should be managed according to standard-of-care.

9.4. Subject Consent

Subjects will be approached to obtain written informed consent prior to any institution non-standard-of-care assessments or study specific data being collected. The purpose of the study and the benefits and risks of participating in the study will be explained to the subject and the consent process must be documented accordingly.

Subjects will be informed that their participation in this study is voluntary and that they may refuse to participate or discontinue from the study at any time. Additionally, subjects will be informed that despite signing informed consent, the screening assessments may demonstrate the subject is not a suitable candidate for the study and may be withdrawn. Subjects will be given the opportunity to ask the investigator questions so that they are adequately informed about the research.

After being informed of the nature of the study, subjects who agree to study participation must sign a written ICF that has been approved by the appropriate Institutional Review Board (IRB) or Ethics Committee (EC) of the respective clinical site. A copy of the signed ICF must be provided to the subject.

For this study, the subject must sign and date the ICF themselves. The use of Legally Authorized Representatives, Healthcare Proxies or any other means of representation will not be permitted.

If new information becomes available that may affect a subject's decision to continue to take part in the study, this information will be discussed with the subject.

The principal investigator or his/her authorized designee must conduct the informed consent process.

9.5. Randomization and Treatment Assignment

Not applicable. There are no treatment arms or randomizations required for this study.

9.6. Medication Compliance

Not applicable. There are no required medications or medication protocols for this study.

9.7. Assessment of Efficacy

9.7.1. Baseline

The following assessments will be performed within 30 days prior to the scheduled ENB procedure:

- Signed informed consent
- Eligibility criteria
- Subject demographics
- Medical history

9.7.2. Procedure Day

The following procedures and assessments will be performed on the day of the index procedure (Day 0):

- Lesion characteristics (e.g., size, location, morphology)
- Procedural information (e.g., technical success, procedure time, biopsy tools, primary and secondary endpoints).

9.7.3. Procedure Details

Details of the index procedure are given below (see also Figure 6).

1. Begin ENB per standard practice.
2. Complete automatic registration and navigate to a position that is within 2.5 cm of the target index lesion.
3. Lock LG in place and conduct local registration with Fluoroscopic Navigation Technology (without moving the catheter).
4. Complete a CBCT scan to document the correct location (prior to any movement of the LG).
5. Complete navigation and position the catheter as appropriate based on the local registration correction.
6. Conduct a second local registration.
7. Conduct a second CBCT.
8. Advance the first biopsy tool.

9. Once in place to biopsy, capture fluoroscopy video sweep with a tool in place (Fluoro "Tool in Lesion"). "In Place" is intended to mean in the location at which tissue sampling would occur.
10. Complete a CBCT scan to confirm that the biopsy tool is accurately positioned in three dimensions within the lesion (CBCT "Tool in Lesion").
11. If available, radial endobronchial ultrasound (rEBUS) may be used to reconfirm the location
12. Complete biopsy sampling per standard size practices.
13. Complete lymph node sampling per standard site practices.

9.7.4. Study Completion

Subjects will complete the study at the completion of the 7-day post-procedure visit. No additional care will be provided to study subjects after completion of the study with respect to this clinical investigation plan (CIP). Standard of care should continue. The reporting window for the 7-day follow-up is 4-7 days.

9.8. Assessment of Safety

Adverse events will be collected after the ENB index procedure has been initiated (defined as introduction of the locatable guide or extended working channel into the subject). Adverse events will be collected immediately post-procedure and at 7-day post-procedure visit, with a window of 4-7 days post-procedure for the 7-day phone call.

The following safety endpoints will be evaluated in all enrolled subjects. These events will be evaluated for their relationship to the study device and study procedure, and classified according to CTCAE Version 5.

- Incidence of all pneumothorax related to ENB index procedure
- Incidence of CTCAE Grade ≥2 pneumothorax related to the ENB index procedure
- Incidence of all bronchopulmonary hemorrhage related to ENB index procedure
- Incidence of CTCAE Grade ≥2 bronchopulmonary hemorrhage related to the ENB index procedure
- Incidence of CTCAE Grade ≥4 respiratory failure related to ENB index procedure

In addition to the Safety Endpoints described above, all Adverse Events related to the superDimension™ navigation system, associated tools, or ENB procedure as described in Section 11.

9.9. Recording Data

This study will utilize an eCRF. The eCRF will be used to capture the required data elements. Medical and study records, rather than eCRFs, will serve as the source documentation.

9.10. Deviation Handling

The Principal Investigator must make every effort to follow the CIP, unless the deviation is necessary in an emergent situation to protect the rights, safety and/or wellbeing of the subject. Deviations from the CIP will be collected on a Protocol Deviation CRF and reviewed with the Principal Investigator to ensure compliance.

The investigator must notify Medtronic and the reviewing IRB/EC of any deviation from the Investigational Plan when specific to the protection of the life or physical well-being of a subject in an emergency. Such notice must be given as soon as possible, but in no event later than five (5) working days after the emergency has occurred.

If a pattern of non-compliance is noted, the study manager will determine the course of action to take, such as root cause, review relevant CIP procedures and as applicable retrain and verify understanding of the issue in question. This will be documented in the Study Master Files. In the case of repeated or serious non-compliance, the Sponsor reserves the right to disqualify the offending site.

9.11. Subject Withdrawal or Discontinuation

Subjects may voluntarily withdraw themselves from the study if they no longer wish to have their study related information used. Additionally, the Principal Investigator may withdraw or choose not to enroll a subject if they feel they do not meet the CIP defined Inclusion and Exclusion Criteria or if it is in the best medical interest of the subject in question.

In cases of voluntary subject withdrawal, all data collected from the time of Informed Consent to the time of Voluntary withdrawal may be used. Additionally, subjects who withdraw or discontinue will not be replaced. Enrollment will continue as per CIP definitions up to the predefined maximum number of subjects.

The reason for study exit of all enrolled subjects will be documented on the applicable electronic case report form (eCRF). In the event the subject withdraws consent during the study, the date of withdrawal will be documented. If the study investigator voluntarily removes a subject from further study participation, supporting documentation must be in place for the rationale and date of removal. Every attempt will be made to contact subjects who are noncompliant. Subjects will be considered lost to follow-up once the following steps have been taken:

- Three phone calls should be made to the subject. Each attempt should be clearly documented in the source documents and the response or lack thereof should be captured.
- If there is no response to the phone calls, then certified letter should be written to the subject. A copy of the letter should be retained in the subject's source document.
- After a period of one (1) week following completion of the above actions, the subject will be considered Lost to Follow-up. The sponsor should be notified and the Study Exit form should be

completed.

10. Risks and Benefits

10.1. Potential Risks

All devices utilized in this study are commercially available. There are no anticipated risks related to inclusion of subjects in this clinical study above and beyond anticipated risks related to any ENB procedure. All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Subject names will be kept confidential.

Addition of the Fluoroscopic Navigation Technology to the superDimension™ Navigation System is not expected to increase the risk of the device beyond the risks previously reported for superDimension™ Navigation System v7.1. Potential risks of the use of the superDimension™ Navigation System for ENB procedures have been evaluated in the superDimension™ navigation system v7.2 Use Failure Modes and Effects Analysis (UFMEA; DHA00036 Rev B, with unchanged risks from DHA00027 Rev I), as well as in the NAVIGATE Clinical Trial Medical Device Reporting (MDR) Reportable Event Trend & Risk Analysis Report for the superDimension™ Navigation System Version 7.2 (DGR00462, Effective28-Sep-2017).

10.1.1. Summary MDR Reportable Event Trend & Risk Analysis Report

The NAVIGATE clinical study (study number NCT02410837) first subject enrollment occurred on April 16, 2015. The objective of the study is to evaluate outcomes following electromagnetic navigation bronchoscopy (ENB) procedures using the superDimension™ navigation system.[39]

An analysis was performed on the MDR reportable events associated with the NAVIGATE study to determine how this information relates to the superDimension™ navigation system v7.2. In this analysis the MDRs associated with NAVIGATE were reviewed for any notable trends and new adverse effects. The reporting period for the analysis ranged from April 2015 through July 2017. During this time there have been 291 reportable events reported by Covidien llc to the FDA. This includes 130 deaths, 3 malfunctions, and 158 serious injuries. The majority of deaths were determined to be primarily related to the patient's condition with no allegations against a Covidien llc Interventional Lung Solutions (ILS) device. The overall adverse event reporting rate for the ILS group during the time period was 1.16% (including the MDRs associated with NAVIGATE).

Risk management procedures and supporting documentation were updated to align adverse effects and occurrence rates observed in the NAVIGATE MDR data. Furthermore, a field experience analysis was performed for the superDimension™ navigation system v7.2 to determine any additional design inputs during development.

A paper published in April 2017 documents the results of the first 1,000 subjects enrolled in the

NAVIGATE study after one-month follow-up.[37] The interim data provides an early look at typical patient and lesion characteristics and procedural standard-of-care. Data demonstrated low adverse event rates in a generalizable population across diverse practice settings.

Overall, no notable trends were identified based on the analysis of the NAVIGATE study MDRs. The report summarizing the first 1,000 subjects at one-month follow-up further demonstrates a safe patient profile for the superDimension™ navigation system.[37] The data generated from the NAVIGATE study was taken into consideration and incorporated during the development of the superDimension™ navigation v7.2 system.

In the majority of cases, the root cause could not be determined as the device was either not returned for analysis or no issues were found during investigation (127). Some cases were attributed to the ENB procedure (15) and patient condition (1) with no allegations against ILS devices or were attributed to non-ILS devices (11).

The most common serious injury reported included pneumothorax (72), bleeding (38), and medical complications (31). Pneumothorax and bleeding are known complications associated with electromagnetic navigation systems. A further breakdown of adverse events by the subject device and investigation results is provided below in **Table 2.**

Please refer to the most current version of the Reportable Event Trend & Risk Analysis Report for additional information.

Table 2. Event Type by Device

Subject Device	Event Type	Internal Investigation Results	Total
System Console	Pneumothorax	Inconclusive – no anomalies identified (28)	40
		Related to procedure (4)	
		Related to non-superDimension Tool (7)	
		Investigation in process (1)	
	Bleeding	Inconclusive – no anomalies identified (14)	19
		Related to non-superDimension Tool (4)	
		Patient Condition (1)	
	Pneumomediastinum	Inconclusive – no anomalies identified (3)	3
	Medical Complication	Inconclusive – no anomalies identified (22)	27
		Related to procedure (5)	
	Respiratory Complication	Inconclusive – no anomalies identified (11)	14
		Related to procedure (3)	
GenCut Core Biopsy Tool	Pneumothorax	Inconclusive – no anomalies identified (1)	2
		Related to procedure (1)	
	Bleeding	Inconclusive – no anomalies identified (2)	4
		Related to procedure (1)	
		Inconclusive – no device information provided (1)	
Biopsy Forceps	Pneumothorax	Inconclusive – no anomalies identified (9)	9
	Bleeding	Inconclusive – no anomalies identified (2)	7
		Inconclusive – no device information provided (3)	
		Investigation in process (2)	
Biopsy Needle	Pneumothorax	Inconclusive – no anomalies identified (5)	7
		Inconclusive – no device information provided (1)	
		Investigation in process (1)	
	Bleeding	Inconclusive – no anomalies identified (4)	5

Table 2. Event Type by Device

Subject Device	Event Type	Internal Investigation Results	Total
		Inconclusive – no device information provided (1)	
	Medical Complication	Inconclusive – no anomalies identified (1)	1
Cytology Brush	Pneumothorax	Inconclusive – no anomalies identified (7)	12
		Inconclusive – no device information provided (5)	
	Bleeding	Inconclusive – no anomalies identified (1)	3
		Inconclusive – no device information provided (2)	
Extended Working Channel	Pneumothorax	Related to procedure (1)	1
	Medical Complication	Inconclusive – no anomalies identified (2)	3
		Inconclusive – no device information provided (1)	
Fiducial Marker	Pneumothorax	Inconclusive – no anomalies identified (1)	1
		Total	**158**

10.1.2. Study-related Imaging

There are risks associated with the use of x-ray fluoroscopy and CBCT imaging for this study.

A milliSievert (mSv) is a unit of radiation dose. The average effective radiation dose during a typical bronchoscopy procedure with fluoroscopic guidance is approximately 0.5 mSv[40] up to 2 mSv per scan. The typical radiation dose from a chest CBCT scan is estimated at 0.98-1.15 mSv.[41] Up to approximately 3 fluoroscopy sweeps and 3 CBCT scans will be conducted during the study procedure. Thus, the total radiation exposure from this study is estimated at up to 9-10 mSv. It should be noted that radiation dose will vary based on the type of imaging system used and the size of the patient.

For comparison, the average dose from natural sources of radiation is approximately 3 mSv per year from natural background radiation, such as radon and cosmic rays. In higher elevation areas the background exposure can be as high as 10 mSv per year. The annual allowable dose for radiation workers (e.g., x-ray technicians) is 50 mSv.

The probability for absorbed x-rays to induce cancer or heritable mutations leading to genetically associated diseases in offspring is thought to be very small for radiation doses of the magnitude that are associated with CT procedures. For any one person, the risk of radiation-induced cancer is much smaller than the natural risk of cancer. However, the risk of harmful effects may increase if a patient is exposed to additional procedures that involve radiation such as x-rays or additional CT scans required during

standard of care.

10.2. Potential Benefits

Outside of the normal ENB procedure, the study may or may not be of benefit to the study subjects. The data collected from this study will help to collect new information on the accuracy of the Fluoroscopic Navigation Technology feature and future system enhancements.

10.3. Risk-Benefit Rationale

Every effort will be made to minimize the risks discussed in Section 10.2, as these risks are standard for this procedure. There will be minimal change to the execution of the ENB procedure as it relates to the planning, ENB guidance of associated procedural biopsy tools or method of sampling. It is more likely that the addition of the fiducial board will improve visibility and provide a reference of measurement for areas of interest.

Additional design elements to reduce risk and burden to the subject are described in Section 6.2.

11. Adverse Events and Device Deficiencies

11.1. Definitions/Classifications

Adverse event definitions used in this study are based on ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects -- Good Clinical Practice; https://www.iso.org/obp/ui/#iso:std:iso:14155:ed-2:v1:en), which is aligned with MEDDEV 2.7/3 Revision 3, May 2015 (Guidelines on Medical Devices, Clinical Investigations: Serious Adverse Event Reporting).

Adverse events will be collected after the point of enrollment (defined as introduction of the locatable guide into the subject). Adverse events (AEs) will be monitored until a subject completes the study. Any unresolved procedural or device related events that are still ongoing past study exit will be monitored by the physician per their institutional standard of care.

In addition to the Safety Endpoints described in Section 5.4, all Adverse Events related to the superDimension™ navigation system, associated tools, or ENB procedure.

Anticipated adverse events are listed in Section 10.1.

11.1.1. Adverse Event (AE)

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

NOTE 1: This definition includes events related to the superDimension™ Navigation System v7.2 with Fluoroscopic Navigation Technology and all superDimension™ tools and accessories.

NOTE 2: This definition includes events related to the procedures involved, including bronchoscopy and sedation.

Events occurring in users or other persons related to the medical device will not be collected for the purposes of this study.

11.1.2. Serious Adverse Event (SAE)

For the purposes of this study, a Serious Adverse Event is an adverse event that has

1. Led to death,
2. Led to serious deterioration in the health of the subject, that either resulted in
    a. A life-threatening illness or injury, or
    b. A permanent impairment of a body structure or a body function, or
    c. In-patient or prolonged hospitalization, or
    d. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

NOTE 2: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.

11.1.3. Adverse Device Effect (ADE)

An Adverse Device Effect is an adverse event related to the use of an investigational medical device.

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

11.1.4. Serious Adverse Device Effect (SADE)

A Serious Adverse Device Effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

11.1.5. Unanticipated Serious Adverse Device Effect (USADE)

An Unanticipated Serious Adverse Device Effect (USADE) is defined as serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

11.1.6. Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequate labelling.

11.1.7. Adverse Event Relationship Classification

Causality assessments define the relationship between the use of the medical device (including the procedure) and the occurrence of each adverse event. During causality assessment activity, clinical judgment shall be used and the relevant documents, such as the MDR Reportable Event Trend & Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

Each AE and SAE will be classified according to five different levels of causality. The following definitions will be used to assess the relationship of the serious adverse event to the investigational medical device, accessory devices, or procedures:

- *Not related*: Relationship to the device or procedures can be excluded when:
    - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures
    - the event has no temporal relationship with the use of the investigational device or the procedures;
    - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
    - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;

- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
- harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

- *Unlikely: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.*
- *Possible: The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.*
- *Probable: The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.*
- *Causal relationship: The serious event is associated with the investigational device or with procedures beyond reasonable doubt when:*
  - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
  - the event has a temporal relationship with investigational device use/application or procedures;
  - the event involves a body-site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;
  - the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
  - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
  - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
  - harm to the subject is due to error in use;

- the event depends on a false result given by the investigational device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Events will be distinguished between the serious adverse events related to the device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of device use/application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the sponsor remains uncertain about classifying the serious event, it should not exclude the relatedness and classify the event as “possible”.

11.1.8. Adverse Event Outcome Classification

Outcome of the event will be defined according to the following:

- Fatal: If death was possibly, probably, or causally related to the event
- Not recovered / not resolved: Subject has exited the study and the AE is ongoing and not expected to resolve
- Recovered / resolved: The event has fully resolved prior to study exit
- Recovered / resolved with sequelae: The event has resolved prior to study exit, but retained pathological conditions resulting from the prior disease or injury
- Recovering / resolving: The subject has exited the study and the AE is ongoing but expected to resolve
- Unknown: The subject has exited the study and the AE outcome is unknown

11.2. Reporting of Adverse Events

Assessment of the occurrence of an AE will be based on changes in the subject’s physical examination, laboratory results, and/or signs and symptoms. AEs will be monitored until a subject completes the study. Any unresolved procedural or device related events that are still ongoing past study exit will be monitored by the physician per their institutional standard of care. AEs will be documented in the applicable source documentation and reported on an AE eCRF. To the extent possible, the event to be recorded and reported is the event diagnosis as opposed to event outcome (e.g., death) or symptoms (e.g., fever, chills, nausea and vomiting in the presence of a clinically diagnosed infection is to be reported as infection only).

The following should not be considered an AE:

- A condition requiring a preplanned procedure unless the condition worsened since enrollment
- A preexisting condition found as a result of screening, unless the condition has worsened since enrollment.

For purposes of this protocol, the following occurrences are considered to be expected observations following bronchoscopy procedures (primarily associated with anesthesia) and will not be considered AEs, as long as the event is not associated with significant sequelae, does not prolong hospitalization, and responds to standard medical therapy:

- procedure transient nausea determined to be procedure related and resolving within 4 days after the procedure
- Post procedure transient emesis determined to be procedure related and resolving within 3 days after the procedure
- Post procedure constipation, determined to be procedure and/or medication related
- Post procedure pain that the study investigator considers common and expected post procedure

All responses to the above events that require treatment beyond the institution's standard procedures will be reported as AEs.

11.2.1. Notification to Authorities

The following events are generally considered reportable during the course of this study and should be reported within the timeframes outlined in **Table 3**:

- any AE or SAE
- any Device Deficiency
- new findings/updates in relation to already reported events

Table 3. Reporting of Adverse Events

Type	Report to	Reporting Timeframe (from time of learning of event)
Device Deficiency	Sponsor	Not to exceed 10 working days
AE	Sponsor	Not to exceed 10 working days
	IRB/EC	Per IRB/EC reporting requirements
SAE	Sponsor	Not to exceed 10 working days
	IRB/EC	Per IRB/EC reporting requirements

Events will be reviewed by sponsor or designee to determine any reporting obligations to National Competent Authorities and IRB/EC.

Any Adverse Event will be recorded on the **Adverse Event CRF.**

12. Data Review Committees

There will be no Data Monitoring Committee, Clinical Events Committee or Adverse Events Advisory Committee needed for this post-market feasibility study.

13. Statistical Design and Methods

All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.2 or higher, SAS Institute Inc. Cary, NC) or other widely accepted statistical or graphical software.

Descriptive statistics will be used to present the data and to summarize the results. Continuous variables will be summarized with number of subjects (n), mean, standard deviation, median, and ranges. Categorical variables will be summarized by frequencies and percentages.

The sample size of this feasibility study is not based on power calculations of a statistical hypothesis test.

The following endpoints will be evaluated in Technically Successful cases (those with local registration complete):

- Primary Endpoint: The measured ability of the superDimension™ Navigation System v7.2 with Fluoroscopic Navigation Technology to place the center of the virtual navigation target (green ball) on the intended target lesion as confirmed by CBCT.
- Secondary Endpoint: Percentage of cases in which the intended lesion is correctly identified (as opposed to a non-target lesion or normal lung tissue) as indicated by the system software.

- Secondary Endpoint: Relational Accuracy in cases in which the Intended lesion is targeted.

All other endpoints and safety outcomes will be evaluated in all enrolled subjects.

The following analyses will be conducted:

- Interim Analysis: Will be conducted after the first 5 procedures have been completed for the purpose of evaluating workflow and data validity.
- Final Analysis: Will be conducted after all subjects have completed the procedure for the purpose of evaluating the primary and secondary endpoints.

There are no pre-planned subgroup analyses. Any post-hoc subgroup analyses will be exploratory in nature for the purpose of evaluating the safety and performance of the study device under various clinical conditions.

Due to the post-market and observational nature of the study, no imputation is planned for missing data in the primary and secondary endpoints, if any. All available data from enrolled subjects will be reported.

A detailed Statistical Analysis Plan (SAP) will be prepared prior to data analysis.

Any deviations from this analysis plan will be documented in the final clinical study report.

14. Ethics

14.1. Statement(s) of Compliance

This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, as well as with ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice) and the International Conference on Harmonisation (ICH) of Technical Requirements For Registration of Pharmaceuticals For Human Use, ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 (R1). The principles of the Declaration of Helsinki have all been implemented by means of the subject informed consent process, EC approval, study training, clinical study registration, preclinical testing, risk benefit assessment, and publication policy.

Pediatric, legally incompetent, or other vulnerable subjects are not eligible for the study.

The clinical investigation will not begin until all necessary approvals/favorable opinions are obtained from the appropriate IRB/ECs or regulatory authority, as appropriate. Should an IRB/EC or regulatory authority impose any additional requirements, they will be followed.

Information regarding the study and study data will be made available via publication on clintrials.gov. Additionally, the results of this study will be submitted for publication in an appropriate journal.

No insurance or compensation will be provided to study subjects.

Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the IRB/EC.

15. Study Administration

15.1. Monitoring

Site visits will be conducted by an authorized Medtronic representative to inspect study data, subjects' medical records, and CRFs in accordance with current ICH GCPs and the respective local and national government regulations and guidelines (if applicable). The study investigator and the investigating site will permit authorized clinical research personnel and clinical monitors from Medtronic and/or designee(s) employed by Medtronic to review completed CRFs, IRB decisions, and Investigator, clinical site records, and facilities relevant to this study at regular intervals throughout the study per the monitoring plan. Additionally, subject charts and clinical records will be requested and reviewed so that protocol adherence and source documentation can be verified.

The accuracy and quality of the data obtained from the investigator and maintained by the Sponsor will be confirmed through a structured program of clinical field auditing and internal review detailed in the monitoring plan. In instances where data protection regulations prohibit the direct examination of hospital records by the study Sponsor or designee(s), the Investigator will cooperate in a system of source data verification with the Sponsor. Monitoring may be performed with in person visits or remotely, when applicable.

To ensure the rights, safety, and welfare of study subjects are being maintained, the monitor will maintain assurance that all study staff are trained on the CIP and use of the study devices. If the monitor discovers that an investigator is not complying with the signed Clinical Trial Agreement, the investigational plan, applicable laws, or any conditions of approval imposed by the reviewing IRB or Competent Authority, the monitor will report to the Sponsor and take such steps necessary to promptly secure compliance. If compliance cannot be secured, the investigator's participation in the investigation may be terminated.

Because there are no required medications for this study or other subject-generated reporting requirements, monitoring of subject compliance is not applicable to this study.

For the purpose of this study, 100% of Endpoint Related data will be monitored. This is intended to include all data related to the calculation of the Primary or a Secondary Endpoint, as well as any data related to a Safety Event.

15.2. Data Management

This study will utilize an electronic database and eCRF. All data requested on the eCRF are considered required. Data points not collected and/or recorded will be considered deviations unless otherwise specified. No data points will be collected directly on the CRF.

In order to accurately collect all information, subject worksheets may also be provided for study specific data (specific procedure data points, etc.) not found in the medical records and will be considered the source document.

The Principal Investigator must ensure the accuracy and completeness of the recorded data and then provide his/her electronic signature on the appropriate CRFs. The Investigator's signature for specific CRFs will be documented in compliance with local regulations. Changes to data previously submitted to the sponsor will require a new electronic signature by the Investigator to acknowledge/approve the changes.

Visual and/or computer data review will be performed to identify possible data discrepancies. Manual and/or automatic discrepancies will be created in the Oracle remote data capture (RDC) system and will be issued to the site for appropriate response. The site staff will be responsible for resolving all discrepancies in the database.

15.3. Direct Access to Source Data/Documents

The investigator(s)/institution(s) will permit inspection and study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), including direct access to source data/documents.

15.4. Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will be kept confidential. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document, it must be obliterated.

Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the sponsor, IRBs, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

Subjects will also be informed that information regarding the study that does not include subject identifiers will be posted on www.clinicaltrials.gov.

If the results of the trial are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified.

15.5. Liability

Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the IRB.

15.6. CIP Amendments

Should any amendment to the CIP be required, the CIP Author will collect and review all proposed updates. These will be incorporated as needed and approved per the CIP Approval Process.

15.7. Record Retention

The investigator will maintain the records of the study including all pertinent correspondence, the CIP with any/all amendments, all correspondence with and approval from the IRB, the clinical investigation agreement, the Clinical Trial Agreement, individual subject records, and signed ICFs. Subject files and other source data must be kept for a period of not less than two (2) years after the date on which this investigation is terminated or completed.

Records may need to be maintained by the study investigator for a longer duration if national regulations require or if agreed to in writing with Medtronic. All data and documents should be made available if requested by relevant authorities.

15.8. Publication and Use of Information

The Medtronic Publication and Authorship Policy is aligned with the International Committee of Medical Journal Editors (ICMJE) recommendations (www.icmje.org). The Sponsor will seek to publish, in appropriate peer-reviewed journals and scientific conferences, results of clinical studies where human subjects are involved, regardless of outcome. While study results are owned by the Sponsor, all data on which a publication is based will be made available to all authors as required for their participation in the publication process. Furthermore, data may be published or used by study investigators provided that such publication or use is in accordance with this protocol, the Medtronic Publication and Authorship Policy, and the Clinical Investigation Agreement. Investigators must submit a copy of all manuscripts and/or abstracts to the Sponsor for review and comment 30 days prior to planned submission. Medtronic acknowledges that its right to review and comment shall relate solely to the proprietary, licensing, and/or confidential rights Medtronic may have in such proposed publication, rather than whether such results and/or opinions are favorable to Medtronic.

The publication of substudies, post-hoc analyses, regional results, or single-center experiences based on multicenter clinical studies should not precede that of the primary multicenter publication, and should cite the primary publication whenever possible, as required by specific journal and scientific meeting guidelines.

Medtronic involvement in a publication (e.g., funding of the study; sponsor of the study; collection, analysis, and interpretation of data; professional writing assistance) must be disclosed according to journal-specific policies, submission requirements, and prevailing editorial standards, in addition to those specified by International Committee of Medical Journal Editors. Authors must ensure that an acknowledgement/disclosure statement is included in the body of the manuscript for Medtronic to review for accuracy. All authors must also disclose financial or personal affiliations that could be considered conflicts of interest as per journal/conference requirements.

To enable health care providers, payers, and patients access to the wealth of Medtronic's research, Medtronic will report its scientific data in accordance with the principles outlined in the Guidance Document on Registration and Reporting Results of Company-Sponsored Clinical Trials, Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) and the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11, January 18, 2017).

15.9. Suspension or Early Termination

Medtronic reserves the right to discontinue the study at any stage, with suitable written notice to the investigator, the reviewing IRB, and applicable regulatory agencies. Similarly, the investigator may withdraw from the study at any time, subject to providing written notification to Medtronic 30 days prior to the date they intend to withdraw. However, Medtronic and the investigator will be bound by their obligation to complete the follow-up of subjects already participating in the study. The subjects must be followed according to the clinical protocol, and information obtained shall be reported to Medtronic on the appropriate CRF.

Once the study is complete at the site, the investigator must submit a final report to their IRB and the sponsor per their IRB requirements.

15.10. Study Contact Information

Clinical Research	Medical Affairs
Scott Chouinard PhD Senior Director, Clinical Research Medtronic MITG Surgical Innovations 15 Hampshire Street Mansfield, MA 02048 [redacted]	Jennifer Mattingley MD Medical Affairs Director Lung Health, Surgical Innovations Minimally Invasive Therapies Group 161 Cheshire Lane, Suite 100 Plymouth, MN 55441 [redacted]

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[redacted]

18. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not applicable (new document)	Sean Pidgeon, Senior Clinical Research Specialist Kristin Hood, Senior Principal Medical Writer