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Document Cover Page

Study: NAVIGATE

Official Title: NAVIGATE: Cli***n***ica***l*** E***v***aluation of superD***i***mension™ Navi***ga***tion System for Elec***t***romagn***e***tic Navigation Bronchoscopy

ClinicalTrials.gov ID: NCT02410837

Document Type: Study Protocol that includes Statistical Analysis Plan

Date of Document : 17-NOV-2015 (version 2.1)

1.0 Title Page

Clinical Investigational Plan (CIP) INFORMATION	
Title:	NAVIGATE: Cli***n***ic***a***l E***v***aluation of superD***i***mension™ Navi***ga***tion System for Elec***t***romagn***e***tic Navigation Bronchoscopy
CIP Number:	COVENBP0475
Version Date:	November 17, 2015
Version:	2.1
Sponsor Representatives:	[redacted] Medtronic 15 Hampshire Street Mansfield, MA 02048 USA [redacted]

This investigational plan contains confidential information for use by investigators participating in the Medtronic Clinical Evaluation of the superDimension™ Navigation System for Electromagnetic Navigation Bronchoscopy study (NAVIGATE). It should be maintained in a secure location. It should not be copied or made available for review by any unauthorized person or firm.

Summary of Changes to CIP			
Version	**Section**	**Description of Change**	**Reason for Change**
1	N/A	N/A	N/A
1.1 (EU only)	9.2	Removed the example statement on Investigator eligibility for roll-in subjects example of conducting less than 5 ENB procedures in last 30 days.	Clarification on eligibility for roll-in subjects. Final determination of eligibility for roll-in cases will be assessed during the qualification process. At this time, Version 1.1 is for Europe only.
2.0	4.0, 8.2.2, 8.6.4.3, 8.6.5	Added ENB Productivity and Activity Questionnaire (ENB-PAQ) to the 1-month visit.	It is beneficial to obtain a subject's assessment of how the ENB procedure affects their work productivity and activities.
2.0	4.0, 8.2.2	Added "other lung disease" to the secondary diagnosis endpoints.	The study has the ability to capture and report on this information.
2.0	4.0, 5.2, 8.2.2	Clarified the secondary endpoint on adequacy for molecular testing.	The purpose of the endpoint surrounded the adequacy of sample collection, rather than the testing itself.

2.0	4.0,8.4.2	Removed the portion of the exclusion criteria on the pregnancy test.	Females who are pregnant or nursing should not participate in the study, but sponsor will leave it up to the institutional policies/standard of care if they will require pregnancy tests.
2.0	5.2, 8.4, 11.0	Procedure time changed from bronchoscope in/out to locatable guide in/out.	This change adequately captures the actual procedure of ENB, and leaves out other procedures that could occur at the same visit.
2.0	8.3	Changed the requirement of an investigator to be medically licensed rather than board certified.	Board certification language was part of the template CIP. For purposes of this study, having a Medical License is sufficient.
2.0	8.6.4.1, 8.6.5	Moved smoking history into the medical history assessment. Clarified what medical histories would be collected.	Since smoking history is part of a medical history, and other aspects of a medical history are to be collected, clarification on medical history was made.
2.0	8.6.4.3	Removed the requirement of the 1-month visit to be conducted in person, and added the allowance of 1-month visits to be conducted via phone.	A 1-month post procedure visit is not typically standard of care for most sites. This is affecting enrollment and subject returns for 1-month visit. All 1-month visit data can be easily collected via phone.
2.0	9.3	Lowered the maximum enrollment per site from 250 to 75.	This was to help the study to collect data at a wide range of different sites. Certain regions may decide to have a lower cap for their region.
2.0	n/a	Minor updates (such as contact information) and minor clarifications were made throughout the protocol. These minor changes did not affect the purpose or requirements of the study.	Minor updates and clarifications were needed in the protocol to meet global regulatory requirements or to provide contact updates or to make minor corrections.
2.1	4.0, 8.2.2, 8.6.4.3, 8.6.5	Changed the name of the added questionnaire “Electromagnetic Navigation Bronchoscopy Productivity and Activity Questionnaire (ENB-PAQ)”	Name change required.

2.0 Principal Investigator Signature Page

Principal Investigator Signature Page

Title:	NAVIGATE: Cli***n***ic***a***l E***v***aluation of superD***i***mension™ Navi***ga***tion System for Elec***t***romagn***e***tic Navigation Bronchoscopy
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I, the undersigned, have read and understood the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol and in accordance with the relevant laws/regulations and standards outlined in the Clinical Investigation Agreement.

Name	Signature	Date

3.0 Table of Contents

4.0 Protocol Synopsis

Background and Rationale of the Study	
Study Objective	The objective of this prospective, single-arm, multicenter, post-market, observational, study is to evaluate outcomes following electromagnetic navigation bronchoscopy (ENB) procedures using the superDimension™ navigation system.
Test Device	superDimension™ Navigation System
Control or Comparator	Not applicable
Study Design	
Study Type	Prospective, single-arm, multicenter, post-market, observational
Study Phase	Post-market
Study Location	Global
Planned Follow-Up	All subjects will be followed for 24 months
Planned # of Subjects	Up to 2,500 globally
Planned # of Sites	Up to 75
Primary Endpoint	The primary endpoint is the incidence of pneumothorax related to the ENB index procedure rated as Grade 2 or higher according to the Common Terminology Criteria for Adverse Events (CTCAE) scale.
Secondary Endpoints	The following secondary endpoints will be evaluated for all ENB index procedures: 1. Incidence of all pneumothorax related to ENB index procedure 2. Incidence of bronchopulmonary hemorrhage related to ENB index procedure rated as Grade 2 or higher according to

	CTCAE scale 3. Incidence of respiratory failure related to ENB index procedure rated as Grade 4 or higher according to CTCAE scale 4. Subject health status evaluated by EQ-5D questionnaire at all visits 5. Subject satisfaction evaluation at 1-month visit 6. ENB procedure effect on subject productivity and activity using the ENB Productivity and Activity Questionnaire (ENB-PAQ) at 1-month visit The following secondary endpoints will be evaluated for all ENB index procedures performed for suspicion of cancer or other lung diseases in a lung lesion: 7. Diagnostic yield 8. Sensitivity 9. Specificity 10. Positive predictive value (PPV) 11. Negative predictive value (NPV) 12. Repeat biopsy rate due to lack of diagnosis during ENB index procedure 13. Adequacy of sample for molecular testing and mutation type (if applicable) 14. Diagnosis 15. Stage at diagnosis (if applicable) The following secondary endpoint will be evaluated for all ENB index procedures conducted for placement of fiducial markers: 16. Success rate of accurate placement of fiducial markers demonstrated through follow-up imaging. The following secondary endpoint will be evaluated for all ENB index procedures conducted for dye marking in preparation for surgical resection. 17. Success rate of dye marking demonstrated by successful surgical resection The following secondary endpoint will be evaluated for all ENB index procedures conducted for a lymph node biopsy: 18. Success rate of obtaining lymph node biopsy to provide stage of diagnosis.

Randomization	Not applicable
Follow-Up Schedule	Subjects will be evaluated at baseline, procedure, 1 month, 12 months, and 24 months post-index ENB procedure.
Eligibility Criteria	Inclusion Criteria 1. Subject presents with lung lesion(s) requiring evaluation 2. Subject is willing and able to provide informed consent to participate in the study 3. Subject is candidate for elective ENB procedure 4. Subject is over the age of 18 Exclusion Criteria 1. The subject is unable or unwilling to comply with study follow-up schedule 2. The subject has participated in an investigational drug or device research study within 30 days of enrollment that would interfere with this study 3. Female subjects who are pregnant or nursing as determined by standard site practices
Statistics	
Endpoint Analyses	Study data will be summarized as descriptive statistics (counts and percentages).
Determination of Sample Size	No formal sample size estimates were conducted. The study is predefined to include up to 2,500 subjects.
Interim Analyses	Interim analyses will be conducted as defined in the publication plan. All interim analyses will be based on complete data for the specified follow-up timepoint.
Pre-Planned Subgroup Analysis	Subgroup analysis of the study endpoints on multiple subsets of study subjects based upon variables such as geography, demographics, investigator experience, and lesion and procedure characteristics are planned.

5.0 Acronyms and Definitions

5.1 Acronyms

eCRF	electronic case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
EC	ethics committee
ENB	electromagnetic navigation bronchoscopy
EP	existing patient
GCP	good clinical practice
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IFU	instructions for use
IRB	institutional review board
NCI	National Cancer Institute
NP	new patient
NPBI	New patient, brief interaction (<6 visits and no inpatient hospitalization)
NPCC	New patient, continued care
NPV	negative predictive value
PAQ	Productivity and Activity Questionnaire
PPV	positive predictive value
RDC	remote data capture
SAE	serious adverse event
SAP	statistical analysis plan
TNM	Revised International System for Staging Lung Cancer Classification System
TTNA	transthoracic needle aspiration

5.2 Definitions

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:

- Grade 1: Mild symptoms; intervention not indicated
- Grade 2: Moderate symptoms; medical intervention indicated
- Grade 3: Transfusion, radiologic, endoscopic, or operative 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)

Diagnostic Test Evaluations

- **Diagnostic Yield**: the proportion of cases that yield a definitive diagnosis. Diagnostic yield will be calculated per patient (as the denominator) and not per the number of lesions biopsied if multiple lesions were biopsied in a single ENB procedure.
- Where a=true positive, b=false positive, c=false negative, and d=true negative:
    - **Sensitivity**: Probability that an ENB-guided biopsy will be positive when malignancy is present (true positive rate): = a / (a+c)
    - **Specificity**: Probability that an ENB-guided biopsy will be negative when malignancy is not present (true negative rate): = d / (b+d)
    - **Positive predictive value (PPV)**: Probability that malignancy is present when an ENB-guided biopsy is positive: = a / (a+b)
    - **Negative predictive value (NPV)**: Probability that malignancy is not present when an ENB-guided biopsy is negative: = d / (c+d)

Existing Patient (EP)

Defined as subjects under care by treating institution more than 30 days prior to the ENB index procedure

Lesion Size

Defined as greatest diameter of target lesion

Navigation Accuracy

Distance between tip of the locatable guide and the targeted lung lesion (not done for lymph nodes)

Navigation Success

The proportion of cases in which the operator is able to successfully navigate to the lung target with ENB guidance

Navigation Time

Total time that locatable guide is used in the subject during the ENB procedure

New Patient (NP)

Defined as subjects new to treating institution within 30 days of the ENB procedure and referred by physicians not affiliated with treating institution

NPs will be further categorized as:

- Those with a brief interaction (BI) with treating institution (<6 visits and no inpatient hospitalization): NPBI
- Those who undergo continued care at treating institution: NPCC

Peripheral Lung Lesion

A lesion that is located in the outer third of the lung and difficult to reach by traditional bronchoscopy

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:

- 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

Procedure Time

Time between initial introduction of the Locatable Guide into the body and final removal of the Locatable Guide

Repeat biopsy rate due to lack of diagnosis during ENB index procedure

Additional biopsy or biopsies conducted after the ENB-guided index procedure, required due to insufficient tissue collection for diagnosis at the index procedure.

Respiratory Failure

A disorder characterized by impaired gas exchange by the respiratory system resulting in hypoxemia 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:

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

Stage

Lung cancer staging will be defined according to the Revised International System for Staging Lung Cancer (TNM) Classification System (1, 2). Refer to Appendix 17.2, NAVIGATE_Lung Cancer Staging.

Tissue Adequacy

Tissue adequacy is defined as the proportion of cases in which tissue obtained during the ENB index procedure is adequate for subtyping of lung cancer and molecular testing when appropriate

6.0 Introduction

6.1 Background/Justification of Investigation

Rapid and precise diagnosis of suspicious lesions is crucial to determine the optimal treatment for lung disease. Diagnosis of peripheral lung lesions, which comprise 25-30% of all lung lesions, is particularly challenging (3, 4).

Technologies that allow for earlier diagnosis and treatment of malignant lung disease are crucial for improving survival rates. According to the American Cancer Society's 2014 estimates, the survival rate for distant (metastasized) lung cancer is 4%, compared to 26% for regional cancer and 54% for localized cancer (5).

Electromagnetic navigation bronchoscopy (ENB)™ is an image-guided approach that uses 3D-reconstructed computed tomography (CT)-scan and sensor location technology to guide a steerable endoscopic probe to peripheral lung lesions that may be beyond the reach of conventional bronchoscopes (5-7).

Over 24 original research articles have been published describing outcomes following ENB to aid in the diagnosis of peripheral lung lesions and mediastinal lymph nodes (3, 6-28). Diagnostic yield aided by ENB in these studies has ranged from 59.0% to 94.0%, with rates generally higher in more recent analyses (3, 6, 9, 10, 15, 17, 18, 20, 23-25).

ENB is also associated with a more favorable safety profile than alternative techniques; in a meta-analysis of 15 studies representing data from over 1000 lung nodules, the pneumothorax

rate after ENB was only 3.1% (29). In comparison, in a meta-analysis of 19 studies, the median pneumothorax incidence rate following CT-guided transthoracic biopsy was 25% (range 4% to 60%) (30).

Despite these promising results, outcomes following ENB are widely varied and most evidence to date is based on single-center analyses (21 of the 24 published studies) with only 3 studies enrolling greater than 100 subjects (see Table 1). The impact of user/center experience, patient risk factors, and lesion characteristics remains largely unexplored in a large multi-center study. In addition, further information is needed about the use of ENB to place dye markers to allow biopsy and surgery in the same procedure, the use of ENB to place fiducials to enable radiation therapy, the adequacy of cells and tissue captured using ENB for genomic testing, the impact of ENB on stage of diagnosis, and the cost effectiveness of ENB.

The proposed post-market study will enroll up to 2,500 consecutive subjects at up to 75 sites worldwide, making it the largest prospective ENB clinical study to date. The 24-month follow-up of this study will also allow an assessment of the correlation between stage of diagnosis and long-term survival rates, in contrast to most prior ENB studies that evaluated only diagnostic yield and acute complication rates.

The objective of this prospective, single-arm, multicenter, post-market, observational, study is to evaluate outcomes following electromagnetic navigation bronchoscopy (ENB) procedures using the superDimension™ navigation system.

6.2 Report of Prior Investigations

6.2.1 Biocompatibility Evaluation

Biocompatibility testing was performed on all components of the product to demonstrate that the materials used are acceptable for the intended use. Biological safety testing has been successfully completed for the relevant device components; the devices are compliant with EN ISO 10993-1:2009 standard and FDA guidelines.

6.2.2 Clinical Studies

Results of 24 original research articles describing outcomes following ENB to aid in the diagnosis of peripheral lung lesions and mediastinal lymph nodes are summarized below. Based on the data in the table, the diagnostic yield weighted mean is 73.6% overall, 69.0% for studies published between 2005 and 2010, and 78.5% for studies published between 2011 and 2014. The overall pneumothorax weighted mean rate is 3.0%.

Table 1. Prior Clinical Studies

Study Lead Author and Citation	Study Design	N Pts.	Diagnostic Yield (%) Aided by ENB	Pneumothorax (%)
Balbo PE (6)	Retrospective, non-consecutive, single-center, single-arm	40	70.7	0.0
Becker HD (7)	Prospective, consecutive, single-center, single-arm	29	69.0	3.4
Bertoletti L (8)	Prospective, single-center	53	77.4	4.0
Brownback KR (9)	Retrospective, consecutive, single-center, single-arm	55	74.5	0.0
Diken ÖE (10)	Prospective, randomized, single-center	94	72.8	0.0
Eberhardt R (11)	Prospective, multi-center, randomized controlled trial	39	59.0	5.0
Eberhardt R (12)	Prospective, single-center	53	67.0	2.3
Eberhardt R (13)	Prospective, non-consecutive, multi-center, single-arm	89	75.5	1.9
Gildea TR (14)	Prospective, single-center, pilot study	58	74.0	3.5
Jensen KW (15)	Retrospective, consecutive, multi-center, single-arm	92	65.0	3.3
Karnak D (16)	Prospective	21	85.7	4.8
Karnak D (17)	Prospective, consecutive, single-center, single-arm	76	89.5	3.9
Khan AY (18)	Prospective, single-center, single-arm	24	75.0	0.0
Lamprecht B (19)	Retrospective, consecutive, single-center, single-arm	13	76.9	0.0
Lamprecht B (20)	Prospective, consecutive, single-center, single-arm	112	83.9	1.8
Loo FL (3)	Retrospective, consecutive, single-center, single-arm	40	94.0	0.0
Mahajan AK (21)	Retrospective, single-center, single-arm	48	77.0	10.2
Makris D (22)	Prospective, consecutive, single-center, single-arm	40	62.5	7.5
Mohanasundaram U (23)	Retrospective, single-center, single-arm	41	89.0	13.0
Odronic SI (24)	Retrospective, consecutive, single-center, single-arm	91	85.7	5.3

Table 1. Prior Clinical Studies

Study Lead Author and Citation	Study Design	N Pts.	Diagnostic Yield (%) Aided by ENB	Pneumothorax (%)
Pearlstein DP (25)	Retrospective, consecutive, single-center, single-arm	101	85.0	5.8
Schwarz Y (26)	Prospective, controlled, single-center	13	69.2	0.0
Seijo LM (27)	Prospective, consecutive, single-center, single-arm	51	67	0.0
Wilson DS (28)	Retrospective, consecutive, single-center, single-arm	248	69.8	1.2

Diagnostic yield defined as the proportion of subjects in whom ENB-directed biopsy yielded a diagnosis, as reported in the original article

7.0 Identification and Description of Device

7.1 Device Description

The superDimension™ navigation system is an image-guided localization system used to navigate endoscopic tools to targets in the lungs, such as lymph nodes and solitary pulmonary nodules. The superDimension™ navigation system consists of several reusable (non-sterile) hardware components used for ENB. A picture of the main console and a list of system components are shown below in Figure 1.

Localization system

- System cart
- Isolation transformer
- Location subsystem
- Uninterruptable power supply
- Industrial personal computer
- Touch screen monitor
- Location board
- Patient sensor triplet
- Sensor patches
- Keyboard
- Mouse
- Remote control
- Foot pedal

Currently available guiding catheter and accessory tools

- Locatable guide
- Extended working channel
- Edge locatable guide
- Edge extended working channel
- Edge extended working channel firm tip
- Bronchoscope adaptor
- Bronchoscope clip
- Patient sensors
- Localization components

Figure 1. superDimension™ Navigation System and Components

7.2 Indication and Contraindications

The System User Manual and the applicable *Instructions for Use* (IFU) will be the primary source of information for the system and components and will be kept current at each site throughout the study.

For detailed information regarding the indicated use of the device and contraindications, please refer to the System User Manual and applicable IFU(s).

7.3 Identification

The superDimension™ navigation system available at the clinical site will be used to conduct all ENB procedures. The system must have software version 6.0 or higher.

8.0 Study Design

Up to 2,500 consecutive subjects who undergo an ENB procedure using the superDimension™ navigation system will be enrolled at up to 75 global clinical sites. Consecutive subjects who

meet the eligibility criteria, sign informed consent, and undergo an ENB procedure using the superDimension™ navigation system will be included in the study. Subjects will be evaluated at baseline, procedure, 1 month, 12 months, and 24 months.

8.1 Study Objective

The objective of this prospective, single-arm, multicenter, post-market, observational, study is to evaluate outcomes following ENB procedures using the superDimension™ navigation system.

8.2 Endpoints

This post-market study is intended to capture clinical outcomes related to the real world use of ENB including but not limited to peripheral lesion biopsies, lymph node biopsies, fiducial market placement for radiation therapy, and tumor marking for diagnostic and therapeutic surgery.

The primary endpoint was chosen as a comprehensive safety endpoint that would be applicable to all ENB procedures being conducted as part of this study. The secondary endpoints are a combination of both safety and effectiveness endpoints that will be categorized in relation to intent of the ENB procedure being conducted.

8.2.1 Primary Endpoint

The primary endpoint is the incidence of pneumothorax related to the ENB index procedure rated as Grade 2 or higher according to the CTCAE scale.

8.2.2 Secondary Endpoints

The following secondary endpoints will evaluated for all ENB index procedures:

1. Incidence of all pneumothorax related to ENB index procedure
2. Incidence of bronchopulmonary hemorrhage related to ENB index procedure rated as Grade 2 or higher according to CTCAE scale
3. Incidence of respiratory failure related to ENB index procedure rated as Grade 4 or higher according to CTCAE scale
4. Subject health status evaluated by EQ-5D questionnaire at all visits
5. Subject satisfaction evaluation at 1-month visit
6. ENB procedure effect on subject productivity and activity using the ENB Productivity and Activity Questionnaire (ENB-PAQ) at 1-month visit

The following secondary endpoints will be evaluated for all ENB index procedures performed for suspicion of cancer or other lung diseases in a lung lesion:

7. Diagnostic yield
8. Sensitivity
9. Specificity

10. Positive predictive value (PPV)
11. Negative predictive value (NPV)
12. Repeat biopsy rate due to lack of diagnosis during ENB index procedure
13. Adequacy of sample for molecular testing and mutation type (if applicable)
14. Diagnosis
15. Stage at diagnosis (if applicable)

The following secondary endpoint will be evaluated for all ENB index procedures conducted for placement of fiducial markers:

16. Success rate of accurate placement of fiducial markers demonstrated through follow-up imaging.

The following secondary endpoint will be evaluated for all ENB index procedures conducted for dye marking in preparation for surgical resection.

17. Success rate of dye marking demonstrated by successful surgical resection

The following secondary endpoint will be evaluated for all ENB index procedures conducted for a lymph node biopsy:

18. Success rate of obtaining lymph node biopsy to provide stage of diagnosis.

8.3 Selection of Investigational Centers and Training Requirements

For this study, the following center selection criteria will be utilized.

- The center must have superDimension™ navigation system with Version 6 software or higher
- The center must have sufficient patient population, defined as the ability to perform at least five (5) ENB procedures per month
- There are no other ongoing studies that would prevent center from achieving enrollment goals
- The center has adequate research staff to conduct the study
- The center must be willing and able to comply with the Clinical Investigational Plan and data reporting requirements
- The center must be willing to enroll consecutive eligible subjects
- The center must have experience and/or ability to utilize the electronic data capture system
- The investigator(s) must be medically licensed
- The investigator(s) must have completed or be willing to complete the superDimension™ navigation system training course conducted by Medtronic

Physicians in training (surgical residents, fellows) and Physician Assistants may assist the study investigator in the procedure as per standard procedures and practices at his/her institution; however, a study investigator must be the primary operator during the ENB procedure.

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.

Medtronic will maintain a list of sites and investigators who are participating in the study; this information will be available on www.clinicaltrials.gov.

8.4 Subject Selection and Enrollment

After being informed of the nature of the study, the subject will sign a written informed consent form (ICF) that has been approved by the appropriate Institutional Review Board (IRB) or Ethics Committee (EC) of the respective clinical site. Following signing the informed consent form, the point of enrollment is defined as the time at which the ENB procedure is started. The start of the ENB procedure is defined as time of initial introduction of the Locatable Guide into the body.

Up to 2,500 subjects will be enrolled in the study at up to 75 sites. Subjects' participation in the study will last approximately 24 months

The ENB procedure will be performed per the System User Manual, applicable product 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.

8.4.1 Inclusion Criteria

1. Subject presents with lung lesion(s) requiring evaluation
2. Subject is willing and able to provide informed consent to participate in the study
3. Subject is candidate for elective ENB procedure
4. Subject is over the age of 18

8.4.2 Exclusion Criteria

1. The subject is unable or unwilling to comply with study follow-up schedule
2. The subject has participated in an investigational drug or device research study within 30 days of enrollment that would interfere with this study
3. Female subjects who are pregnant or nursing as determined by standard site practices

8.5 Withdrawal 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:

- Two 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 two (2) weeks 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.

8.6 Study Procedures

8.6.1 Screening and Informed Consent

A baseline visit will be performed within 30 days prior to the scheduled procedure to assess study eligibility. 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 in the medical record. Subjects who agree to study participation must sign an IRB/EC approved ICF. 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. A copy of the signed ICF must be provided to the subject.

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.

8.6.2 Screen Failures

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 eCRFs. Screen Failures will not be counted towards the number of study subjects.

8.6.3 ENB Procedures

The ENB procedure should be conducted in accordance with the System User Manual, applicable IFU and local institution standard of care.

8.6.4 Study Schedule

Subjects will be evaluated at baseline, procedure, 1 month, 12 months, and 24 months post-index ENB procedure, as detailed below and in Table 2. All study data will be reported on the appropriate subject eCRFs.

8.6.4.1 Baseline

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

- Signed informed consent
- Eligibility criteria
- Demographics
- Medical history (including smoking history, lung history, anticoagulant and anti-platelet therapy medications, and risk factors)
- Quality of life questionnaire assessment utilizing EQ-5D

8.6.4.2 Procedure

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

- Procedural information
- Lesion characteristics (if applicable)
- Biopsy results (if applicable)
- Adverse event assessment
- Lung cancer assessment
- Healthcare utilization

8.6.4.3 1 Month

It is preferred that the 1-month visit be conducted as in-person visit; however it will be acceptable to obtain the required information through a telephone visit with the subject. Additionally, a systematic review of the subject's medical records should be evaluated to ensure that all information is accurately reported.

The following procedures and assessments will be performed 1 month (±7 days) post-index procedure:

- Adverse event assessment
- Lung cancer assessment
- Healthcare utilization
- Repeat biopsy results (if applicable)
- Quality of life assessment utilizing EQ-5D
- Patient satisfaction assessment

- Productivity and activity assessment using the ENB-PAQ

8.6.4.4 12 and 24 Months

It is preferred that the 12 and 24 month visits be conducted as an in-person visit. However, it will be acceptable to obtain the required information through a telephone visit with the subject. Additionally, a systemic review of the subject's medical records should be evaluated to ensure that all information is accurately reported.

The following procedures and assessments will be performed 12 months (±30 days) and 24 months (±30 days) post-index procedure:

- Adverse event assessment
- Lung cancer assessment
- Healthcare utilization
- Repeat biopsy results (if applicable)
- Quality of life assessment utilizing EQ-5D

8.6.5 Study Assessments Table

Table 2: Table of Assessments

	Baseline (Day -30 to 0)	Procedure (Day 0)	1 month (±7 days)	12 months (±30 days)	24 months (±30 days)
Informed consent	X				
Eligibility criteria	X				
Demographics	X				
Medical history	X				
Procedural information		X			
Lesion characteristics (if applicable)		X			
Adverse event assessment		X	X	X	X
Lung cancer assessment		X	X	X	X
Healthcare utilization		X	X	X	X
Biopsy results (if applicable)		X	X	X	X
EQ-5D questionnaire	X		X	X	X
Patient satisfaction assessment			X		
ENB-PAQ			X		

9.0 Statistical Analysis

A separate statistical analysis plan (SAP) will be maintained to describe statistical methods and data analysis procedures.

9.1 General

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. In general, data for all study subjects combined will be presented. Individual data will be presented in subject listings.

Descriptive statistics will be used to present the data and to summarize the results. Discrete variables will be presented using frequency distributions and cross tabulations. Continuous variables will be summarized by presenting the number of observations (N), mean, standard deviation, median, minimum, and maximum values.

In general, data analysis will be conducted on all subjects who are enrolled in the trial and undergo an ENB procedure utilizing the superDimension™ navigation system. Analyses will be conducted on multiple subsets of study subjects based upon variables such as geography, demographics, investigator experience, lesion and procedure characteristics, and other variables as deemed appropriate. Results from interim and final analyses will be presented and/or published as defined in the Publication Plan.

9.2 Roll-in Subjects

For participating investigators who meet investigator selection criteria but do not have extensive experience conducting ENB procedures utilizing the superDimension™ navigation system, the investigator may be allowed to perform “roll-in cases”. A maximum of five (5) 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.

Final determination of eligibility for roll-in cases will be assessed as part of the investigator qualification process and will be documented in the study files.

Roll-in subjects will be considered study participants and will complete all protocol-required procedures and exams. However, data for the roll-in population will be analyzed separately from the remaining study population in an effort to detect any differences of outcomes related to level of investigator experience.

9.3 Sample Size Determination

No formal sample size estimates were conducted. The study is designed to include up to 2,500 subjects.

Each site will be allowed to enroll a maximum of 75 subjects into the study.

9.4 Analysis of Baseline Demographics and Procedural Characteristics

Descriptive statistics will be generated for pre-intervention demographics, procedural characteristics, and follow-up data collected. Categorical variables will be analyzed using frequency, incidence, and event rate. For continuous variables collected in the study, analysis will include mean, median, standard deviation, and range.

9.5 Endpoint Analysis

For the primary and secondary endpoints, descriptive statistics will be provided. The endpoints will be summarized using frequency measures such as count and percentage. For the primary endpoint, a 2-sided 95% exact binomial confidence interval will also be provided.

Adverse events for all enrolled subjects will be collected and reported for each follow-up visit. For adverse event reporting, which includes the primary and secondary endpoints, the primary analysis will be based on subject counts (e.g., the number and percentage of subjects with event among the total number of Subjects). The data will be presented in the format of p% (x/N) [e], with p and x being the percentage and number of subjects with events, respectively, N being the sample size of the analysis population, and e being the total number of events occurred in the x subjects. For example, the data of 2% (20/1000) [38] indicates that a total of 38 events occurred in 20 subjects out of a total of 1000 subjects (2%).

9.6 Handling of Missing Data

For the primary endpoint, the assessment is done peri-procedurally and it is projected that there will be minimal reduction in the eligible population based on the time of the measurement. Therefore, no imputations are planned for the primary endpoints.

9.7 Analysis Populations

Clinical data will be assessed in the following subject groups. Additional groups, such as country specific populations, may be assessed as deemed appropriate.

1. *Roll-in cohort*: defined as subjects identified as “roll-in subject” upon study enrollment (see Section 9.2).
2. *Primary cohort*: defined as all subjects who are enrolled in the trial and undergo and ENB index procedure utilizing the superDimension™ navigation system minus roll-in subjects
3. *Overall cohort*: defined as all subjects who are enrolled in the trial and undergo and ENB procedure utilizing the superDimension™ navigation system

9.8 Interim Analysis

Interim analyses will be conducted as defined in the publication plan. All interim analyses will be based on complete data for the specified follow-up timepoint. All interim analyses must be pre-specified and approved by the steering committee.

At a minimum, the following interim analyses will be conducted:

1. First 500 primary cohort subjects undergo ENB index procedure and complete the 1-month follow-up visit
2. First 1,000 primary cohort subjects undergo ENB index procedure and complete the 1-month follow-up visit
3. First 1,500 primary cohort subjects undergo ENB index procedure complete the 1-month follow-up visit

Additional interim analyses may be performed as appropriate.

9.9 Pre-planned Subgroup Analysis

It is planned to evaluate the primary and secondary endpoints on multiple subsets of study subjects based upon variables such as geography, demographics, investigator experience, lesion and procedure characteristics, and other variables as deemed appropriate. The subgroup analyses are exploratory in nature, for the purpose of evaluating the safety and effectiveness performance of the study device under various clinical conditions.

10.0 Risk/Benefit Analysis

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. Outside of the normal procedure, the study may or may not be of benefit to the study subject. The data collected from this study will help to establish new information on the ENB procedure and the diagnosis and treatment of lung lesions.

10.1 Risks of ENB

Rex et al. performed a systematic review and a meta-analysis of ENB for the evaluation of peripheral lung lesions. A total of 15 studies, representing data from 1,033 lung nodules, were included. A total of 32 pneumothoraces were reported (3.1%), of which 17 (1.6%) required chest tube drainage. Nine cases of minor or moderate bleeding were reported, none requiring treatment or intervention. Other reported complications were 1 self-limited hematoma event and 1 episode of hypercapnic respiratory failure attributed to sedation (29).

Table 1 in Section 6.2.2 above lists pneumothorax rates in ENB studies published in the Rex meta-analysis, with the addition of more recently published ENB studies (24 studies in total). The weighted mean pneumothorax rate specifically for ENB procedures based on the data provided in Table 1 is 3% (range 0% to 13%).

11.0 Adverse Events & Complications

Adverse events will be collected after the ENB index procedure has been initiated (defined as introduction of the Locatable Guide into the subject). During the course of the study, the following AEs will be collected and reported on the eCRF:

- All AEs related to the superDimension™ navigation system, associated tools, or ENB procedure (both index and any subsequent repeat ENB procedure)
- All deaths
- All pneumothoraxes
- All bronchopulmonary hemorrhages
- All respiratory failures

11.1 Adverse Event (AE)

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

NOTE: Documented pre-existing conditions are not considered to be reportable AEs unless there is a change in the nature or severity of the condition.

11.2 Serious Adverse Event (SAE)

A serious AE (SAE) is an AE that has

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function, or

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to fetal distress, fetal death or a congenital abnormality or birth defect

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the study, without serious deterioration in health, is not considered a serious AE.

11.3 Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect (UADE) is an adverse event related to the study device which by its nature, incidence, severity or outcome has not been previously identified in product risk analysis.

11.4 Adverse Event Relationship Classification

Relationship to study product administration will be determined as follows:

- *Not related*: No relationship between the AE and the administration of study treatment and a known relationship to other etiologies such as concomitant medications, surgical procedure or subject's clinical state.
- *Related:* An AE that follows a plausible temporal sequence from administration of the study treatment and follows a known response pattern to the study treatment. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
- *Impossible to Determine:* Given the information available, sequence and timing of events, it is impossible to determine the relationship of the AE with the study treatment.

11.5 Adverse Event Outcome Classification

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

- *Resolved:* The event has fully resolved.
- *Continuing:* The event is ongoing.

11.6 Adverse Event Recording

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 symptoms (e.g., fever, chills, nausea and vomiting in the presence of a clinically diagnosed infection is to be reported as infection only).

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:

- Post 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.

11.7 Adverse Event Reporting

Please refer to Table 3 for a list of the minimum AE reporting requirements for investigators. If local regulations or IRB/EC require faster reporting, then the investigator will adhere to those requirements.

Table 3: Investigator AE Reporting Requirements

Type	Report to	Reporting Timeframe (from time of learning of the event)
Adverse Event	Sponsor	Recommended within 10 working days
	IRB/EC	Per IRB/EC reporting requirements
Serious Adverse Event	Sponsor	Recommended within 24 hours, required within 10 working days
	IRB/EC	Per IRB/EC reporting requirements
Unanticipated Adverse Device Effect	Sponsor	Recommended within 24 hours, required within 10 working days
	IRB	Required within 10 working days
	EC	Per EC reporting requirements

Events will be reviewed by Medtronic or designee to determine any reporting obligations to FDA or Competent Authorities as well IRB/EC. Reporting will occur within the timelines per local regulations and requirements.

12.0 Device Deficiencies

A device deficiency is an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

All superDimension™ navigation system (including associated accessories and tools) device deficiencies will be documented on the appropriate eCRF and the device should be returned to Covidien for analysis, if possible. Instructions for returning the device will be provided. Device deficiencies should also be documented in the subject's medical record.

Device deficiencies are NOT to be reported as AEs. However, if there is an AE that results from a device deficiency, that specific event would be recorded on the appropriate eCRF.

12.1 Medical Monitor

The Sponsor will utilize a Medtronic Medical Monitor to provide a medical review and adjudication of pre-specified AEs in support of protocol defined endpoint data. The Medical Monitor will be a qualified, board-certified physician that is not affiliated with an investigative center.

During the review of AEs, the Medical Monitor will be not be blinded to the treatment and investigational site.

13.0 Ethics and Compliance

13.1 Statement of Compliance

This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guideline (ICH GCP), and any regional or national regulations, as appropriate. All principles of the Declaration of Helsinki have been implemented in this clinical study by means of the patient informed consent process, IRB/EC approval, clinical study training, clinical study registration, publication policy, etc.

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

13.2 Protocol Compliance

No changes to the protocol will be permitted without the written approval from Medtronic and the IRB/EC. 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. Except in such an emergency, prior written approval by Medtronic is required for changes in or deviations from the Plan. If these changes or deviations affect the scientific soundness of the Plan or the rights, safety, or welfare of human subjects the IRB/EC will also be notified. All other deviations will be reported per the site's IRB/EC deviation policy. Should any deviations from the Investigational Plan occur, these will be reviewed by Medtronic for their clinical significance. If the event is performed without written approval from all parties, the investigator may be terminated from the study.

13.3 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's identifying number will be collected on 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, IRB/ECs, 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 clinicaltrials.gov.

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

13.4 Data Access and Publications

The Medtronic Publication and Authorship Policy is aligned with the International Committee of Medical Journal Editors (ICMJE) recommendations (www.icmje.org). Medtronic 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 Medtronic, 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 this protocol, the Sponsor's Publication and Authorship Policy, and the Clinical Investigation Agreement. Investigators must submit a copy of all manuscripts and/or abstracts to Medtronic 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 Under FDAAA 2007 (Title VIII).

13.5 Role of the Steering Committee

The Steering Committee will consist of Investigators participating in this study, as well as appropriate members of Medtronic Clinical and Medical Affairs. The role of the Steering Committee is to make recommendations on the design and conduct of the study, the analysis of data, and the communication of results in alignment with the Sponsor's Publication and Authorship Policy.

14.0 Monitoring Procedures

Site visits will be conducted by an authorized Medtronic representative to inspect study data, subjects' medical records, and eCRFs 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 eCRFs, IRB/EC 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 Medtronic will be confirmed through a structured program of clinical field auditing and internal review detailed in the monitoring plan. The timing of site visits and scope of verification requirements will be included in the monitoring plan. 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 review training records to ensure all study staff are appropriately trained. If the monitor discovers that an investigator is not complying with the signed Investigator Agreement, the clinical investigational plan, applicable laws, or any conditions of approval imposed by the reviewing IRB/EC or applicable regulatory 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.

14.1 Data Collection and Processing

This study will utilize an electronic database. All data requested on the eCRF are considered required. Data points not collected and/or recorded will be considered deviations unless otherwise specified. The Principal Investigator must ensure the accuracy and completeness of the recorded data and then provide his/her electronic signature on the appropriate eCRFs.

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

15.0 Study Supplies and Device Accountability

The superDimension™ navigation system (including associated accessories and tools) are commercially available. Sites will obtain devices through standard site procedures for commercially available product. The devices used during study procedures should be used in accordance with approved indication and instructions for use.

There are no study specific device accountability or traceability requirements for this study.

16.0 General Information

16.1 Study Contact Information

Questions regarding safety or medical procedures should be directed to Medical Affairs. All other questions should be directed to Clinical Affairs.

Clinical Affairs	Medical Affairs
[redacted]	[redacted]

16.2 Retention of Records

The investigator will maintain the records of the study including all pertinent correspondence, the study protocol with any/all amendments, all correspondence with and approval from the IRB/EC, the clinical investigation agreement, the Investigator 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 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.

16.3 Study Completion/Termination of Study

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

Medtronic reserves the right to discontinue the study at any stage, with suitable written notice to all investigators, all reviewing IRBs or ECs, and applicable regulatory agencies. Similarly, investigators 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 investigators 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 during subject follow-up shall be reported to Medtronic on the appropriate eCRF.

17.0 References

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18.0 Appendices

18.1 Sample Patient Informed Consent

See attached document, “18.1_NAVIGATE_Sample Patient Informed Consent”

18.2 Lung Cancer Staging

See attached document, “18.2_NAVIGATE_Lung Cancer Staging”

INFORMED CONSENT AND HIPAA FORM

STUDY TITLE: NAVIGATE: Cli***n***ic***a***l E***v***aluation of superD***i***mension™ Navi***ga***tion System for Elec***t***romagn***e***tic Navigation Bronchoscopy™

PROTOCOL No.: COVENBP0475

SPONSOR: Medtronic, Interventional Lung Solutions
161 Cheshire Lane, Suite 100
Plymouth, MN 55441 USA

INVESTIGATOR: Name
Address
Phone Number
Email Address

SITE(S): Name
Address

IRB: Name
Address
Phone Number
Email Address

INTRODUCTION

You are being asked to participate in a clinical research study because you are scheduled, as part of your normal care, to have an electromagnetic navigation bronchoscopy™ (ENB™) procedure using the superDimension™ navigation system. This procedure is not experimental, is approved by the Food and Drug Administration (FDA), and the product is commercially available. This study allows your doctor to record the results of your procedure and subsequent care in an organized manner.

The purpose of this consent form is to help you decide if you would like to participate in this research study. You will be informed of the purpose, procedures including follow up visits, risks and benefits of the study, as well as contact information for any questions you may have. Please read and understand the following informed consent document carefully before signing. Do not sign this form until all of your questions have been answered. You may take an unsigned copy of this form home with you to consider participation or talk about it with family or friends before you decide.

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to evaluate clinical outcomes of electromagnetic navigation bronchoscopy™ (ENB™) procedures using the superDimension™ navigation system.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?
Up to 2,500 patients at up to 75 global sites will take part in the study, including up to 75 subjects at this site. All subjects will be followed for 24 months after the procedure.

WHAT WILL HAPPEN IF I TAKE PART IN THE RESEARCH STUDY?
If you choose to participate in this study, and meet all of the eligibility requirements the following study procedures will take place.

Screening Visit
You will be evaluated within 30 days before your scheduled procedure to assess your eligibility. At this time, you doctor will decide if you qualify, and you will be asked to read, understand, and sign this informed consent document. Additionally, your medical history (including smoking history, risk factors and certain medications) and demographic information will be collected. You will also be asked questions on your quality of life.

Procedure
Your doctor will perform the procedure as planned and any complications will be recorded. During the procedure visit, your general health will be evaluated.

After the procedure visit, you will be required to follow the visit schedule and have examinations performed as listed below.

1 Month Follow-up Visit
At your first follow-up visit, your general health will be evaluated since your last visit. You will also be asked questions on your quality of life, your patient satisfaction and the effect of the ENB™ procedure on your work productivity and activities.

12 Month Follow-up Visit
At your 12 month follow-up visit, your general health will be evaluated since your last visit. You will also be asked questions on your quality of life.

24 Month Follow-up Visit
At your 24 month follow-up visit, your general health will be evaluated since your last visit. You will also be asked questions on your quality of life.

WHAT ARE THE RISKS?
This is an observational study. The risks associated with an observational study are the loss of confidentiality and privacy. All records identifying you will be kept confidential and will not be made publically available to the extent permitted by the applicable laws or regulations.

There are no anticipated risks related to participation in this clinical study above and beyond anticipated risks related to any ENB™ procedure. Your doctor will review the risks of an ENB™ procedure with you.

ARE THERE ANY ADDITIONAL COSTS TO ME?

If you agree to participate in this study, you or your insurance provider will be charged for any procedures that are consistent with the standard of care for this type of procedure. Medtronic will pay for any additional tests or procedures necessary for the study that would not otherwise be a part of your routine clinical care.

If you have any questions or concerns about the cost, coverage or types of tests and procedures that will be conducted, please ask your study doctor.

PAYMENTS
You will not be paid for participating in this study.

WHAT ARE THE BENEFITS?
This study may or may not be of direct benefit to you. However, your participation may help Medtronic to establish additional data on this device for the diagnosis and treatment of lung lesions. Other people may benefit from the results of this study in the future.

ARE THERE ANY ALTERNATIVE TREATMENTS AVAILABLE?
This is not a treatment study. Your alternative is not to have your data from this procedure collected.

WHAT IF I AM INJURED DURING MY PARTICIPATION IN THE STUDY?
If you have side effects from the procedure, you need to report them to your study doctor and your regular doctor, and you will be treated as needed. You or your insurance will be billed for these services. Medtronic has not agreed to pay you if you believe you are injured. You are not, however, waiving any of your legal rights by signing this form. As stated previously, participation in this study does not add any additional risk to you over and above having an ENB™ procedure performed while not in this study.

CAN I WITHDRAW FROM THE STUDY?
Your participation in this study is completely voluntary. You have the right to decline participation or withdraw from the study at any point in time. Choosing to do so will not have any penalties to you, and will not affect the medical care or benefits you receive from your doctor. Your study doctor may also withdraw you from the study if they feel it is in your best interest. In addition, the sponsor may discontinue the study at any time without your knowledge. If this happens, you will be notified.

CONFIDENTIALITY
As part of this study, the study doctor and hospital will keep records of your participation in the study. This section of the consent form describes how your personal information may be used and shared as part of the study. Under federal law, your personal information cannot be used or shared for the study by the Researchers unless you sign this form. You do not have to sign this form. If you do not sign it, you will not be able to be in the study, but it will have no other effect on the medical care you receive.

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

What information about me can be used or shared in the study?

The personal information that may be used or shared is:

- All information collected during the study described in this form, including your gender, age, treatment dates, device identifiers, procedure and test results and other information from your medical records.
- Information in your past medical records that relates to the study.

When you see the phrase "personal information" in this form, it means all of this information.

Who are the Researchers?

As part of the study, your personal information may be kept by the hospital, site and study doctor), and the people who work for them. The people who work with them include the Institutional Review Board, which is a group of people who watch over the study for the hospital. It also includes other employees and contractors who need to see your personal information to help with the study or make sure it is being run right. When you see the word "Researchers" in this form, it refers to all of these people.

Who is the Sponsor of the study?

The sponsor of the study is Medtronic. The Sponsor's employees are the main people who work on the study, but Medtronic may also contract with other companies and people to help it run its business. When you see the word "Sponsor" in this form, it means the company, Medtronic, and any other people or companies helping it.

What can the Researchers do with my personal information?

The Researchers can:

- Use and share your personal information to conduct the study and evaluate the results of the study.
- Use and share your personal information to meet the reporting requirements of government agencies.
- Use and share your personal information to prepare publications or presentations (but no publication about the study will reveal your identity without a different specific, written permission from you).
- Disclose your personal information to the people listed in the next section of this form.
- Remove from your personal information your name and other information that could be used to identify you.
- Use and share your personal information as required by law.

Who can the Researchers disclose my personal information to?

The Researchers can disclose your personal information to people working with any of the following groups:

- The Sponsor of the study;
- Other institutions that are participating in the study;

- Government organizations and other persons (such as the Medical Monitor) who are required to watch over the safety, effectiveness, and conduct of research; and
- Government agencies that have the right to see or review your health information. This includes the Office of Human Research Protections, the Food and Drug Administration, Institutional Review Boards, or similar agencies in other countries.

What can the Sponsor do with my personal information?
After your personal information has been shared with the Sponsor, the Sponsor may use and share it, in the United States or throughout the world, for any of the following reasons:

- To conduct, monitor and audit the study, and to confirm research results;
- To prepare publications or presentations (but no publication about the study will reveal your identity without a different specific, written permission from you);
- For regulatory purposes, such as getting the approval of government agencies to sell products made by the Sponsor;
- To conduct new medical research and develop proposals for new medical products or therapies;
- To share it with government organizations and other persons who are required to watch over the safety and effectiveness of products, therapies, and the conduct of research;
- It may be used and shared as required by law.

Can I decide not to allow the use and sharing of my personal information?
Yes. You do not have to sign this form. However, if you do not sign this form, then you cannot participate in the study.

Can I revoke (take back) my signature on this form?
Yes. You can change your mind about letting your personal information be used or shared at any time by letting the study doctor know in writing. If you change your mind, you will be taken out of the study. No personal information about you will be gathered for the study after that date. However, the personal information gathered before you told the study doctor that you changed your mind may continue to be used or shared by the Researchers and Sponsor if it is needed for the study or any follow-up for the study. If you think it is likely that you will change your mind, please do not sign this form.

Is my personal information protected after it has been disclosed to others?
After the Researchers have shared your personal information with others, including the Sponsor, federal laws may not protect it from being further shared.

Can I see my personal information?
Yes. You may see and copy your information.

Does this form have an expiration (end) date?
The Researchers may use and share your information until the study and any necessary follow-up activities for the study are done. There is no end date for when the Sponsor can use your personal information. If the results of the trial are published, your identity will remain confidential.

NEW INFORMATION
You will be told about anything new that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

WHO CAN I CONTACT WITH QUESTIONS?
If at any time, you have questions regarding this research study please contact your study doctor as noted on the first page.

If at any time you have questions about your rights as a participant, or questions regarding any research related injury, please contact a member of the hospital's Institutional Review Board as noted on the first page

A signed and dated copy of this consent form will be provided to you.

INFORMED CONSENT
I have read this consent form (or it has been read to me). All my questions about the study and my part in it have been answered. I freely consent to be in this research study.
I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form, I have not given up any of my legal rights.

_____
Patient Name (Print)

_____ _____
Signature of Participant **Date**

_____ _____
Signature of Person Obtaining Consent **Date**

Lung Cancer Staging

7th EDITION

Classifications

Primary Tumor (T) Classification

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0 No evidence of primary tumor

Tis Carcinoma in situ

T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus

T1a Tumor 2 cm or less in greatest dimension

T1b Tumor more than 2 cm but 3 cm or less in greatest dimension

T2 Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): involves main bronchus, 2 cm or more distal to the carina; invades visceral pleura (PL1 or PL2); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T2a Tumor more than 3 cm but 5 cm or less in greatest dimension

T2b Tumor more than 5 cm but 7 cm or less in greatest dimension

T3 Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina[1] but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe

T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

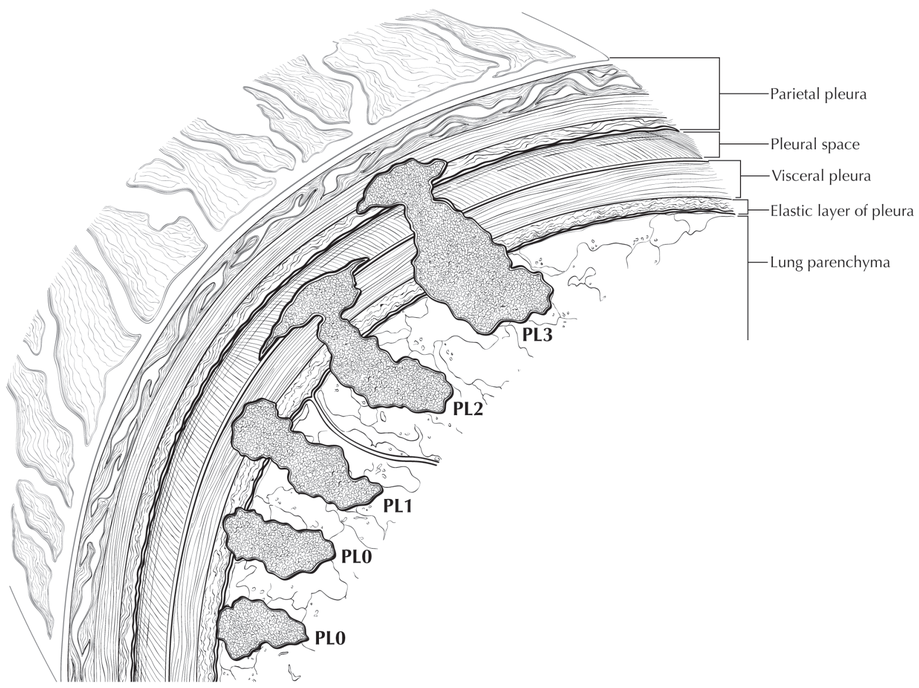
Distant Metastasis (M) Classification

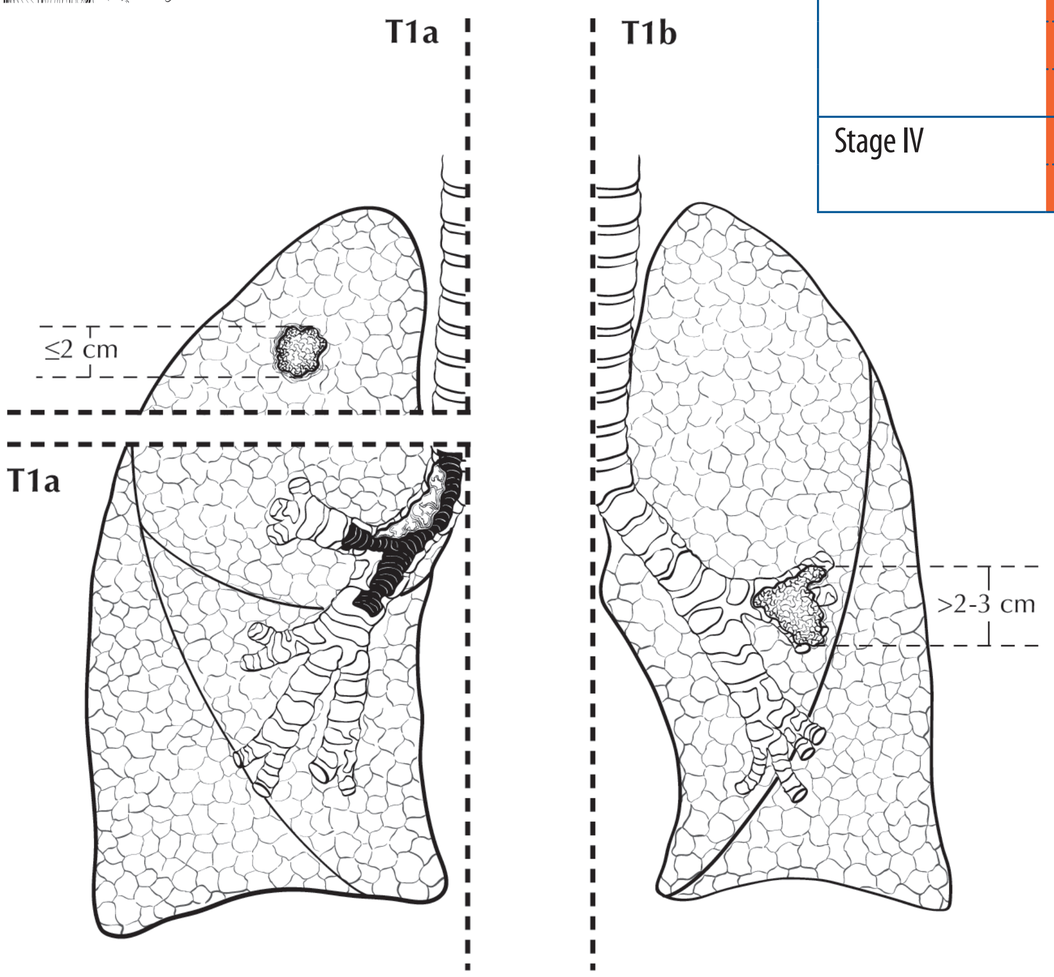
M0 No distant metastasis

M1 Distant metastasis

M1a Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural (or pericardial) effusion

M1b Distant metastasis (in extrathoracic organs)





ANATOMIC STAGE/PROGNOSTIC GROUPS			
Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

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American Joint Committee on Cancer

Lung Cancer Staging

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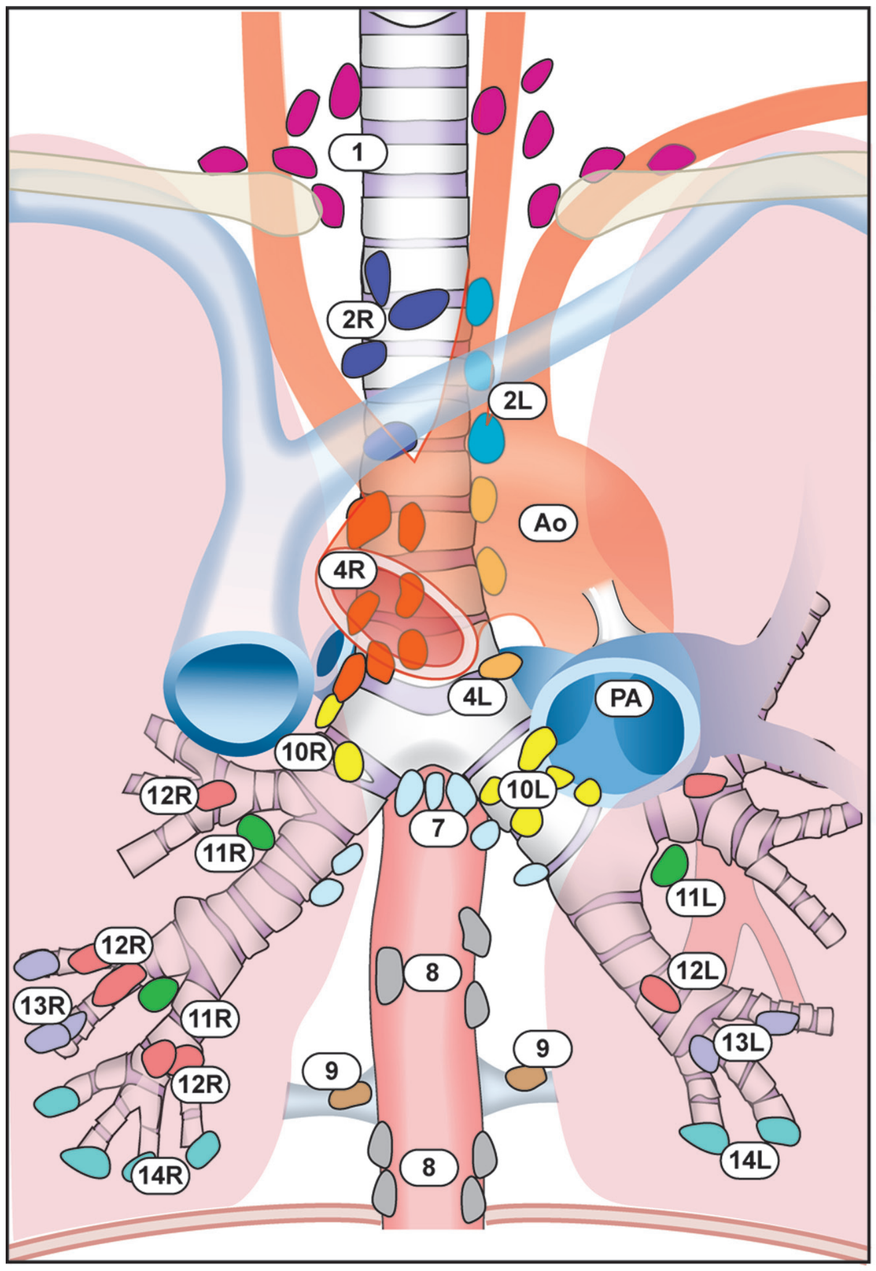

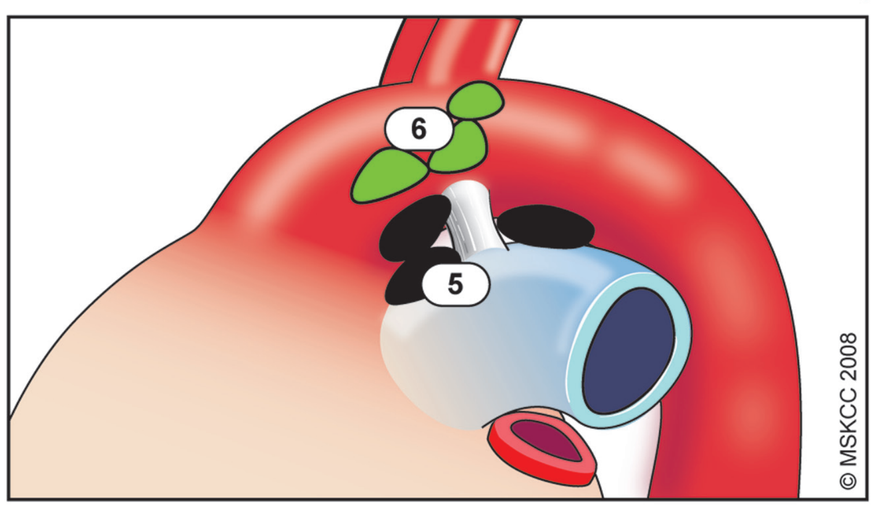

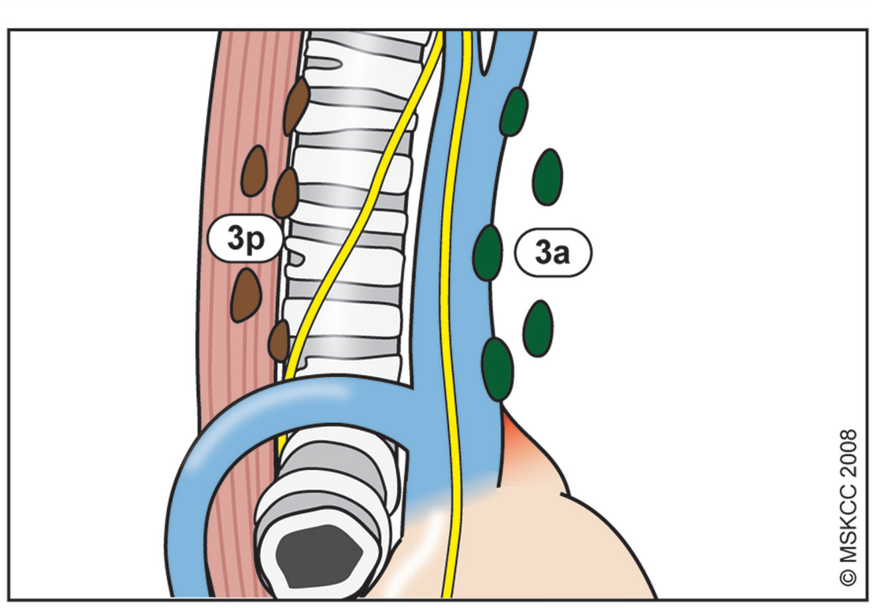

Supraclavicular zone

- **1** Low cervical, supraclavicular, and sternal notch nodes

Superior Mediastinal Nodes

Upper zone

- **2R** Upper Paratracheal (right)
- **2L** Upper Paratracheal (left)
- **3a** Pre-vascular
- **3p** Retrotracheal
- **4R** Lower Paratracheal (right)
- **4L** Lower Paratracheal (left)

Aortic Nodes

AP zone

- **5** Subaortic
- **6** Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

Subcarinal zone

- **7** Subcarinal

Lower zone

- **8** Paraesophageal (below carina)
- **9** Pulmonary ligament

N_1 Nodes

Hilar/Interlobar zone

- **10** Hilar
- **11** Interlobar

Peripheral zone

- **12** Lobar
- **13** Segmental
- **14** Subsegmental

Regional Lymph Node (N) Classification

- **NX** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastases
- **N1** Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
- **N2** Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
- **N3** Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

ILLUSTRATION

The IASLC lymph node map shown with the proposed amalgamation of lymph into zones.

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