Feasibility Study of a Bronchoscopic Ultrasound-Guided Tissue Acquisition System with Real-time Visualization for Collection of Cytology Specimens of Peripheral Pulmonary Lesions

iNod Feasibility

CLINICAL PROTOCOL

PDM# 91122035

Project # E7113

Sponsored By

Boston Scientific Corporation
100 Boston Scientific Way
Marlborough, MA 01752-1234
USA

Contact Information

Role	Contact
Clinical Contact	G Mark Grubb, RN Clinical Project Manager Boston Scientific, Endoscopy Clinical Affairs 100 Boston Scientific Way Marlborough, MA 01752 mark.grubb@bsci.com
Coordinating Principal Investigators	Alex Chen, MD Co-lead Investigator Washington University School of Medicine St. Louis, Missouri Lonny Yarmus, DO Co-Lead Investigator Johns Hopkins University Baltimore, Maryland

Original Release: March 14, 2016

Current Version: March 14, 2016

Protocol Synopsis

Feasibility Study of a Bronchoscopic Ultrasound-Guided Tissue Acquisition System with Real-time Visualization for Collection of Cytology Specimens of Peripheral Pulmonary Lesions	
Objective(s)	To demonstrate feasibility to access, visualize, and obtain specimens adequate for cytology of lung lesions in subjects with suspected lung cancer when using the iNod System.
Planned Indication(s) for Use	The iNod System is intended for use for diagnostic ultrasound imaging and ultrasound-guided fine needle aspiration (FNA) of extramural and submucosal lesions of the tracheobronchial tree.
Test Device	The iNod System, is comprised of the following components: • iNod Ultrasound Imaging System • iNod Ultrasound Catheter • iNod Biopsy Needle • iNod Motor Drive Unit • iNod Sled The iNod Biopsy Needle and the iNod Ultrasound Catheter are intended to be used, in combination, in the Olympus BF-P190 or Olympus BF-MP160 Bronchoscopes.
Study Design	Multi-center, Prospective, Single-arm Feasibility Study with Salvage.
Number of Subjects	5 to 10 Subjects at a study center 15 to 30 Subjects, across all study centers
Number of Centers / Countries	2-3 US Study Centers
Primary Endpoint	Clinical success is defined as the iNod System's ability to acquire adequate specimens of cellular matter suitable for the cytologic evaluation of targeted lung lesions, under real-time visualization. Salvage Procedure: In case of primary endpoint failure with the iNod System, Radial EBUS -guided diagnostic sampling maneuvers (current

Feasibility Study of a Bronchoscopic Ultrasound-Guided Tissue Acquisition System with Real-time Visualization for Collection of Cytology Specimens of Peripheral Pulmonary Lesions	
	standard-of-care) will be performed in an attempt to access, visualize, and sample targeted lung lesions.
Secondary Endpoints	1. Occurrence and severity of Adverse Events related to the iNod System biopsy procedures, as well as Adverse Events related to any subsequent Radial EBUS-guided salvage procedures. 2. Proportion of lesions visualized during iNod Maneuvers 3. Proportion of lesions accessed where iNod Biopsy Needles were deployed in the target lesion during study maneuvers 4. Proportion of iNod maneuvers that acquire specimens of cellular matter for cytology
Study Visit Schedule	Baseline Visit: Informed Consent, Medical History, including collection of a Chest CT image within 6 weeks of study procedure, which confirms the presence of peripheral pulmonary lesion(s). Bronchoscopy Procedure: iNod sampling of lesion followed by additional standard of care (salvage) procedures, should collected specimens be determined as inadequate for cytologic evaluation. Intra-procedural specimens collected for cytology will be documented. Completion / End of Study: • Following the bronchoscopic procedure, and per standard clinical practice, the subject will have a post-procedure chest x-ray. • The subject will have a Day 7 Post-Procedure Safety Call to check for any delayed-onset Device/Procedure/Anesthesia-related safety events.
Study Duration	The study will close after enrollment is completed. The enrollment period is estimated to be open for approximately 1 year from First Patient In (FPI) through Last Patient Out (LPO). Follow-up of unforeseen procedure-related safety events could extend LPO beyond the date of the last study procedure.

Feasibility Study of a Bronchoscopic Ultrasound-Guided Tissue Acquisition System with Real-time Visualization for Collection of Cytology Specimens of Peripheral Pulmonary Lesions	
Key Inclusion Criteria	1. Subject is age 18 years or older. 2. Subject is willing and able to comply with study procedures and provide written informed consent to participate in study. 3. Subject with a predominantly solid lung lesion, 1 cm to 7 cm in diameter, which has been identified on chest CT (obtained within 6 weeks) with the intention to undergo a clinically indicated bronchoscopic evaluation under routine clinical care. If the lesion is partially solid (i.e. there is a ground glass component) then the solid portion must make up 80% of the lesion. 4. Subject for whom the decision to pursue biopsy has been made by the treating physician and agreed upon by the subject.
Key Exclusion Criteria	1. Subjects with pure ground glass opacity, a subsolid target lesion, and/or a ground glass opacity identified on Chest CT. 2. Subjects with lesions that include endobronchial involvement, per Chest CT. 3. Subjects who lack fitness to undergo flexible bronchoscopy and standard of care Radial EBUS-guided cytological assessment evaluations, as determined by the investigator. 4. Subjects with known coagulopathy. 5. Subjects who are pregnant or nursing mothers. 6. Subjects who are currently enrolled in another investigational study that would directly interfere with the current study, without prior written approval from the sponsor.
Statistical Methods	
Primary Statistical Hypothesis	There will be no formal statistical hypothesis tested since this is an observational feasibility study documenting the first human use of the iNod System.
Statistical Test Method	Descriptive statistics will be presented to characterize the trial data and describe the trial results.

Feasibility Study of a Bronchoscopic Ultrasound-Guided Tissue Acquisition System with Real-time Visualization for Collection of Cytology Specimens of Peripheral Pulmonary Lesions	
Sample Size Parameters	Since no formal hypothesis will be tested, there is no statistical justification of sample size. Peripheral pulmonary lesions vary in their location in the tracheobronchial tree, their size, and their characteristics (e.g., concentric vs. eccentric). A sample size of 5-10 subjects per site allows greater potential to evaluate the usability and performance of the system for visualization and sampling this range of lesions. Performance feedback for this traditional feasibility study is sought from more than 1 physician. While staying within the sample size confines of a traditional feasibility study, Boston Scientific has elected to seek the expertise of 2 to 3 interventional bronchoscopists.

Table of Contents

Table of Tables

1. Introduction

This protocol is a traditional feasibility study for the sampling of a peripheral pulmonary lesion in the setting of a suspicion of lung cancer. Standard of practice radial endobronchial ultrasound (R-EBUS) transbronchial needle aspiration (TBNA) is visualizing a peripheral lesion on R-EBUS, locking the placement of the access sheath, removing the ultrasound catheter from the access sheath and then blindly advancing a sampling device to acquire cellular matter for cytologic evaluation. The iNod system performs the same procedure with one fewer device exchange. It provides real-time visualization of the biopsy needle and target peripheral pulmonary lesions during tissue acquisition. The ultrasound probe is not retracted in advance of the sampling maneuver and the sampling is completed under direct visualization. Compared to current standard of care methods for transbronchial sampling of pulmonary lesions, this approach is not expected to add additional risk. Tissue sampling under real-time visualization may improve the efficiency of tissue sampling.

Lung cancer is the most common cancer worldwide; accounting for 1.8 million new cases and 1.6 million deaths in 2012.[1] Lung CA is also the leading cancer killer in both men and women in the United States.[2] The number of deaths caused by lung cancer has increased approximately 3.5 percent between 1999 and 2012 from 152,156 to 157,499. In 2012, there were 86,740 deaths due to lung cancer in men and 70,759 in women.[2] The five year survival rate for lung cancer is 54 percent for cases detected when the disease is still within the lungs. However, only 15 percent of lung cancer cases are diagnosed at an early stage. For distant tumors (spread to other organs) the five-year survival rate is only 4%.[3]

Pulmonary lesions are a common but difficult issue for primary care and specialty physicians and are often found incidentally on Chest X-Ray (CXR) or Computed Tomography (CT) scan.[4] With the results of the National Lung Cancer Screening Trial demonstrating a reduction in lung cancer mortality with screening of high risk patients with low dose CT scan, the number of nodules detected requiring follow up is likely to increase exponentially as 25% of those screened had a detected lung abnormality.[5] In studies of incidentally detected nodules, the prevalence of malignancy ranges from 2-82% [6]. The problem for clinicians is deciding on the management and further diagnostic modalities to pursue.

The various recommended procedures for obtaining tissue diagnosis in these intermediate cases include transthoracic needle aspiration (TTNA), surgery, and flexible bronchoscopy (FB). The diagnostic yield with FB varies with lesion size and location. A lesion having a bronchus sign (the finding of a CT-visible bronchus leading to the lesion) increases the success of transbronchial biopsy and brushing.[7] _ENREF_7 The ACCP recommends that nodules without a CT-bronchus sign should be pursued with TTNA unless radial endobronchial ultrasound (R-EBUS) is available.[8] _ENREF_6 Bronchoscopy is commonly used for pulmonary masses, but the yield, while high, does not approach 100%.

Endobronchial ultrasound (EBUS) and radial EBUS (R-EBUS) are known to be safe and effective imaging techniques for transbronchial and endobronchial biopsy.[9, 10] The location of the bronchoscope at the lesion can be verified with real-time visualization with the guide sheath acting as an extended working channel to maintain the location during R-EBUS

biopsy. Increased use of screening CT scans has led to the increased detection of pulmonary lesions and nodules.

The intent of this clinical study is to demonstrate feasibility to visualize, access, and obtain specimens adequate for cytology of lung lesions in subjects with suspected lung cancer when using the iNod System.

2. Device Description

The iNod system enables real-time visualization and biopsy of peripheral pulmonary lesions by displaying an ultrasound image of the lesion and needle simultaneously. Intended conditions of use are within a pulmonary endoscopy suite or a surgical suite. The iNod System consists of three components (and accessories) that are either identical to or slightly different in design to existing commercially available devices:

- The **iNod Biopsy Needle** is a modified design of the commercially available 25 gauge BSC Expect Slimline Endoscopic Ultrasound Aspiration Needle. The modifications are limited to a modification of the sheath and the addition of a "needle stroke limiter" to the handle. The needle and stylet within the sheath, as well as the handle, remain unchanged.
- The **iNod Ultrasound Catheter** is a slightly modified design of the commercially available BSC OptiCross Coronary Imaging Catheter. The modifications are limited to the absence of the distal guide catheter tip beyond the ultrasound transducer and the absence of a hydrophilic coating on the sheath.
- The **iNod Ultrasound Imaging System** and its two accessories, the **iNod Motor Drive Unit** and the **iNod Sled**, are identical to the commercially available BSC iLab Ultrasound Imaging System and its accessories.

The study system is not approved for commercial use. Local IRB (Institutional Review Board) approval will be obtained at each participating center.

All components of the iNod System are labeled as investigational and include information not limited to name of legal manufacturer, device name and dimensions, lot number, expiration date and investigational use statement.

2.1. Biopsy Needle

The design of the iNod Biopsy Needle is based on the commercially available Boston Scientific 25 gauge Expect Slimline Endoscopic Ultrasound Aspiration (EUS-FNA) Needle (K133312, cleared January 3, 2014), with modifications to allow simultaneous use with the iNod Ultrasound Catheter. The modifications are limited to a modification of the sheath (replacing the single extrusion sheath with a multi-component single-lumen exterior tube) and the addition of a "needle stroke limiter" to the handle. The remainder of the Expect Slimline EUS-FNA Needle design, including the needle, stylet, and handle, is unchanged.

The iNod Biopsy Needle is a 103 cm long (nominal) needle that can be inserted into the working channel of bronchoscope. It is used for fine needle aspiration of lesions within the tracheobronchial tree. The iNod Biopsy Needle consists of a handle assembly and a sheath-covered needle in a single lumen of sufficient diameter to simultaneously accommodate the needle/stylet assembly and the iNod Ultrasound Catheter. The needle has echogenic features at the distal end to facilitate real time visualization of the device under ultrasound. At the proximal end of the sheath, a Y-port with a Tuohy Borst valve allows the iNod Ultrasound Catheter to be inserted into the lumen parallel to the needle. The handle assembly on the proximal end of the device is used to actuate the needle in order to gather specimens. The "needle stroke limiter" on the handle limits the needle extension length to a maximum of 2.5 cm. A stylet is in place within the needle to provide protection to the inside of the sheath during device passage through the bronchoscope. The stylet may also be used to expel the specimen after the procedure. A syringe and stopcock provide and control the vacuum suction to aspirate the specimen, and can be used to expel the specimen after the procedure. The iNod Biopsy Needle retains certain features of the Expect Slimline EUS-FNA Needle upon which it is based that will not be utilized in this study (e.g. sheath and adjustment knob and lock).

2.2. iNod Ultrasound Catheter

The iNod Ultrasound Catheter is a modified design of the OptiCross 40 MHz Coronary Imaging Catheter (K123621, cleared April 15, 2013). The changes to the design are limited to the absence of the distal guide catheter tip beyond the ultrasound transducer and the absence of the hydrophilic coating applied to the shaft of the OptiCross device

The distal guide catheter tip is not necessary for the pulmonary procedure, as a guidewire is not required or used for access, and its presence would limit the depth to which the Ultrasound Catheter could access the tracheobronchial tree. The resulting open distal end does allow flushing saline to empty faster, leading to more frequent replenishment of the flushing saline via the attached 3 cc syringe. The maximum amount of saline expected to enter the airway during the procedure (3 mL) is well below that anticipated to be left behind in the course of a bronchoalveolar lavage (BAL) procedure (30 mL or more), which is recognized as safe.[11] The hydrophilic coating is not required, as it is intended to enhance the pushability of the device during direct tracking through tortuous anatomy. Both the distal guide catheter tip and the hydrophilic coating are applied during the manufacturing process, and their absence does not alter the remaining materials of the device.

The Catheter body comprises a proximal telescoping shaft and a distal shaft. The proximal telescoping shaft and distal shaft compose the usable length of the catheter (135 cm). The proximal telescoping shaft remains outside of the Catheter. The distal shaft serves as a flexible and acoustically transparent imaging window. The proximal telescoping shaft provides pushability to the distal imaging window and serves as a lumen to the imaging core. The telescope assembly allows the imaging core to be

advanced and retracted. The corresponding movement of the transducer occurs from the distal end of the catheter body to the proximal end of the imaging window.

The imaging core consists of a proximal hub assembly and a rotating drive cable that houses a piezoelectric (PZT) transducer at the distal imaging window. The hub assembly (1) provides an electro-mechanical interface between the catheter and the motor drive unit and (2) incorporates a one-way check valve that is used to flush the interior of the catheter body. The catheter must be flushed with saline prior to use, as this provides the acoustic coupling media required for ultrasonic imaging.

The drive cable and PZT transducer rotate independently of the sheath assembly to provide 360° image resolution. The transducer converts electrical impulses sent by the motor drive in to transmittable acoustic energy. Reflected ultrasound signals are converted back to electrical impulses, returned to the motor drive unit, and are ultimately processed by the iNod Ultrasound Imaging System for visualization.

2.3. iNod Ultrasound Imaging System

The iNod Ultrasound Imaging System consists of two compact PC units (one for Image Processing and one for Data Acquisition), a control panel, and a monitor, installed on a cart. The Data Acquisition PC (front-end PC) contains a PCI-based acquisition board that digitizes the RF Ultrasound echo, performs front-end digital signal processing, and direct memory accesses ultrasound frames in vector-based format onto the PCI bus. Once data is saved into host memory, the vector-based frame of data is packetized and sent over a private Local Area Network (LAN) connection onto the Image Processing PC (back-end PC) subsystem.

The Image Processing PC unit represents the back-end image-processing engine. The real-time vector data retrieved from the Data Acquisition PC is unpacked, temporal filtering is executed to reduce transient matters in the frame, and the frame data is converted from vector-based to raster-based frame, which can then be displayed on the monitor.

While the real-time frames are being processed and displayed, the host processor of the Image Processing PC streams raw acquired data and system information onto the system hard drive. This stored raw data may later be converted to DICOM format to be exported to external media such as CD-Rs, DVD+Rs, removable hard disk cartridge, and DICOM network server.

Acquisition, image processing, display, and storage are managed via a graphical user interface-based (GUI) Control panel touch screen, all the same as the iLab Ultrasound Imaging System. The USB-based Control panel touch screen presents a series of software-controlled screens that manage the current imaging case in a structured workflow. The system interfaces with the iNod Motor Drive Unit (MDU), the iNod Sled, and the iNod Ultrasound Catheter. Accessories of the imaging system are as follow:

iNod MDU: The iNod Motor Drive Unit is a non-sterile accessory used with the iNod Ultrasound Imaging System. The iNod Motor Drive Unit (MDU) is identical to the commercially available MDU5 PLUS for the iLab Ultrasound Imaging System. The MDU provides the electro-mechanics for the rotating parts of the iNod Ultrasound Catheter, and the interface between the Catheter and the main console.

iNod Sled: The iNod Sled is a non-sterile accessory used with the iNod Ultrasound Imaging System. The iNod Sled is identical to the commercially available Permanent Sled for the iLab Ultrasound Imaging System. The iNod Sled consists of a cup that holds the iNod Motor Drive Unit (MDU). The sled cup can be freely moved manually in a proximal or distal direction over a 10cm travel distance. When the MDU is placed in to the sled cup, the motordrive engages with the sled drive cone. The motordrive can control the movement of the sled cup, but this functionality is not intended to be used in the clinical investigation.

2.4. Medical Equipment Description

In addition to the iNod System, all pulmonary endoscopy, or surgical suites where the study procedure is being performed must also be equipped with:

- 2.0 mm working channel bronchial scope model numbers Olympus BF-P190 or Olympus BF-MP160F
- Fluoroscopy
- All equipment necessary for Radial EBUS-guided biopsy of peripheral pulmonary lesions.
- Cytological Rapid On-Site Evaluation (ROSE)

All research centers are also required to have on-site capabilities for Chest X-Ray.

3. Objectives

To demonstrate feasibility to access, visualize, and obtain specimens adequate for cytology of lung lesions in subjects with suspected lung cancer when using the iNod System.

4. Endpoints

Primary Endpoint:

Clinical success is defined as the iNod System's ability to acquire adequate specimens of cellular matter suitable for the cytologic evaluation of targeted lung lesions, under real-time visualization.

Salvage Procedure: In case of primary endpoint failure with the iNod System, Radial EBUS -guided diagnostic sampling maneuvers (current standard-of-care) will be performed in an attempt to access, visualize, and sample targeted lung lesions.

Secondary Endpoints:

1) Occurrence and severity of Adverse Events related to the iNod System biopsy procedures, as well as Adverse Events related to any subsequent Radial EBUS-guided salvage procedures.
2) Proportion of lesions visualized during iNod Maneuvers
3) Proportion of lesions accessed where iNod Biopsy Needles were deployed during study maneuvers
4) Proportion of iNod maneuvers that acquire specimens of cellular matter for cytology

5. Design, Scale, and Duration

This study is a multi-center, prospective, single-arm human feasibility assessment.

Treatment of 15-30 subjects will take place at 2-3 clinical centers. No single clinical center will enroll in excess of 10 subjects. As the iNod System is being evaluated as a diagnostic system, study subjects are expected to be consented no more than 2 weeks prior to or up to and including the day of, but prior to, their diagnostic procedure. Subjects will exit the study, post-procedure following a pre-discharge x-ray. In the case of occurrence of a procedure-related Adverse Event, the subject will be followed through event resolution.

6. Subject Selection

6.1 Inclusion Criteria

Subjects who meet all of the following criteria (see Table 6.1-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 6.2) is met.

Table 6.1-1: Inclusion Criteria

Clinical Inclusion Criteria	1) Subject is age 18 years or older. 2) Subject is willing and able to comply with study procedures and provide written informed consent to participate in study. 3) Subject with a predominantly solid lung lesion, 1 cm to 7 cm in diameter, which has been identified on chest CT (obtained within 6 weeks) with the intention to undergo a clinically indicated bronchoscopic evaluation under routine clinical care. If the lesion is partially solid (i.e. there is a ground glass component) then the solid portion must make up 80% of the lesion. 4) Subject for whom the decision to pursue biopsy has been made by the treating physician and agreed upon by the subject.

6.2. Exclusion Criteria

Subjects who meet any one of the following criteria (Table 6.2-1) will be excluded from this clinical study.

Table 6.2-1: Exclusion Criteria

Clinical Exclusion Criteria	1) Subjects with pure ground glass opacity, a subsolid target lesion, and/or a ground glass opacity identified on Chest CT. 2) Subjects with lesions that include endobronchial involvement, per Chest CT. 3) Subjects who lack fitness to undergo flexible bronchoscopy and standard of care Radial EBUS-guided cytological assessment evaluations, as determined by the investigator. 4) Subjects with known coagulopathy. 5) Subjects who are pregnant or nursing mothers. 6) Subjects who are currently enrolled in another investigational study that would directly interfere with the current study, without prior written approval from the sponsor.

7. Subject Accountability

7.1. Point of Enrollment

Point of enrollment is the time at which, following recruitment, a subject signs and dates the informed consent form.

7.2. Withdrawal

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Reasons for withdrawal include physician discretion, subject choice to withdraw consent, loss to follow-up and death. Subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. All applicable case report forms up to the point of subject withdrawal must be completed. Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his/her consent, for whatever reason. All open adverse events should be

closed or documented as chronic. Data collected up to the point of subject withdrawal may be used.

Subjects withdrawn prior to undergoing the diagnostic procedure with the iNod System will not count toward a center's 10 subject limit.

7.3. Enrollment Controls

The risk of over-enrollment is minimized by utilizing a limited number of clinical centers and maintaining close communication with study centers.

8. Study Methods

8.1. Data Collection

Table 8.1-1: Data Collection Schedule

Procedure/Assessment	Study-Specific (iNod) or Standard of Care (SOC)	Screening	Baseline	Procedure	Completion / Study Exit
Informed consent form, including informed consent signature date	**iNod**		X		
Demographics, including date of birth, and gender	**iNod**		X		
Physical Exam	**iNod**				
HCG Pregnancy Testing for women of childbearing potential	**iNod**		X		
Historic Diagnostic Chest CT **Confirmed at enrollment, but per standard of care within 6 weeks of procedure**	**SOC**	X			
Historic PET Results	**SOC**	O			
Medical history	**iNod**		X		
Sedation	**SOC**			X	
iNod System Diagnostic Procedure(s)	**iNod**			X	
iNod Ultrasound (US) Images including lesion visualization and needle visualized in the iNod US Field	**iNod**			X	
Fluoroscopic Images during iNod Maneuver(s)	**iNod**			O	
ROSE (Rapid on-site Evaluation) of obtained specimen (s)	**SOC**			X	
Complete Cytology of obtained specimen(s)	**SOC**			X	X
Standard of Care Diagnostic Procedures (as indicated as required)	**SOC**			O	
Standard of Care US Images including lesion visualization and needle visualized in the iNod US Field	**SOC**			X	
Fluoroscopic Images during Standard of Care Maneuver(s)	**SOC**			O	
ROSE (Rapid on-site Evaluation) of obtained specimen (s)	**SOC**			X	
Complete Cytology of obtained specimen(s)	**SOC**			X	X
Discharge X-ray	**SOC**				X
Device, Procedure, and Anesthesia-related adverse events assessment, including Day-7 Post-Procedure Call	**iNod**			X	X

X = required; O = optional but recommended

8.2. Study Candidate Screening

Potential study candidates will be selected based on the investigator's review of subject referrals for evaluation of their medical history and assessment of candidate's Chest CT, completed within 6 weeks of study procedure, that indicate the presence of a suspected solid peripheral pulmonary nodule between 1cm and 7cm in size.

Only subjects that meet the CT and all other Inclusion Criteria should move forward to the Informed Consent process. All subjects screened and consented will be patients of the investigator(s).

8.3. Informed Consent

Written Informed Consent must be obtained for all subjects who are potential study candidates. Subjects will be asked to sign the Informed Consent form before any study-specific tests or procedures are performed. The Informed Consent form is study-specific and must be approved by the study Institutional Review Board (IRB)/Ethics Committee (EC) and Competent Authority, as applicable.

8.4. Baseline

Must be conducted no more than 2 weeks before or on the day of (preceding) iNod System procedure.

- Informed Consent
- Eligibility Criteria Assessment
- Demographics
- Bronchoscopy History
- Physical Exam including Height & Weight
- Confirmation of a peripheral pulmonary lesion, per historic Chest CT (within 6 weeks of precdure)

Baseline attributes of the target lesion will be recorded:

- Location of Lesion
- Size of Lesion
- Attributes of Lesion (e.g. solid or partial ground glass)

8.5. iNod Diagnostic Procedure

The subject will be prepared for the study procedure under sedation as per current standard or care.

The investigator will perform a bronchoscopic assessment of all lobes of the lung and confirm that there are no contraindications to continue with the iNod System procedure.

iNod System components are supplied to the investigative centers for the conduct of this clinical study by Boston Scientific, free of charge. Each iNod System component will be utilized only to the extent and use limits, defined in the Investigator Brochure. Multiple (a minimum of 4) iNod Ultrasound Catheters and (a minimum of 4) iNod Biopsy Needles are to be available at the commencement of a study procedure.

All iNod System components utilized during a procedure will be recorded, by serial number, to insure device accountability. The model number(s) of the bronchoscope(s) being utilized will also be captured.

The following procedural data will be captured:

- Timing of the total duration of the case, from initial introduction of the bronchoscope to final removal of bronchoscope
- Each iNod Maneuver will be timed from introduction of the iNod Biopsy Needle catheter, pre-loaded with the iNod Ultrasound Catheter, through the removal of the iNod Biopsy Needle.
- Intra-procedural Attributes of the target lesion(s) will be recorded:
    - Location of target lesion (e.g., RB^1, RB^2, RB^3, etc.)
    - Assessment of concentric lesion vs. eccentric lesion
    - Assessment for positive bronchus sign

Imaging to be captured during the iNod System maneuvers, as identified with the serial number of the iNod Imaging System and iNod Biopsy Needle being utilized for each maneuver, will be collected as follows:

- Ultrasound image of the target lesion
- Ultrasound image of the deployed iNod Biopsy Needle at the target lesion
- Supplemental fluoroscopic images, if collected, should also be retained and similarly associated to the specific maneuver by documenting the serial number of the iNod Biopsy Needle being used for that specific procedure

Rapid on-site evaluation (ROSE) will be completed for all obtained specimens. Results will be associated with the serial number of the iNod Biopsy Needle being used for each unique specimen. ROSE interpretations, “adequate (for cytologic evaluation)” or “inadequate (for cytologic evaluation),” will be recorded. Collected specimens will undergo cytologic evaluation following the iNod procedure and final cytologic results will be reported in the study database.

The following situations would indicate the need to abandon the iNod System Procedure and proceed to salvage:

- If the iNod System is unable to physically reach the lesion, as evidenced by the absence of an ultrasound image of the lesion with the iNod System.
- If 3 separate aspirated specimens obtained from the target lesion with the iNod System result in "inadequate (for cytologic evaluation)," the investigator should stop iNod maneuvers and proceed to salvage.

8.6. Salvage Procedure

For study subjects for whom an adequate specimen, defined as a specimen that has been confirmed as suitable for cytologic evaluation, is not obtained from the iNod System diagnostic procedure but for whom continuation with endobronchial maneuvers are not contraindicated, additional standard of care (SOC) R-EBUS-guided diagnostic sampling maneuvers should be conducted.

SOC R-EBUS-guided sampling maneuvers may be conducted utilizing various clinically standard sampling techniques, including but not limited to fine-needle aspiration, brushings, or forceps. Similar to the iNod System procedure, accountability of all SOC devices utilized, timing, ultrasound image(s) of target lesion, fluoroscopic images of lesions and sampling device, as available, ROSE, and Final Cytology should be captured.

8.7. Study Completion

Post-procedure, subjects will be followed through their discharge chest x-ray following their iNod System procedure.

Verbal contact is to be made with the the subject by a member of the site study team 7 (+/- 1) days post-procedure. The purpose of this call is for the study team to assess for any late-occurring study procedure-related or study device-related safety events.

8.8. Source Documents

Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document.

Table 8.8-1: Source Documentation Requirements

Requirement	Disposition
Historic Chest CT Report	Scanned de-identified file for upload in eCRF
Evidence of Medical History that all Inclusionary and Exclusionary elements were confirmed at	Remain on-site

Table 8.8-1: Source Documentation Requirements

Requirement	Disposition
Baseline.	
Procedure Records	Remain on-site
Procedure Worksheets inclusive of devices used per maneuver (by lot or serial number) and timing of each maneuver, both for iNod System and Standard of Care (as indicated) maneuvers	Remain on-site
Cytology Report(s) • Rapid on-Site Evaluation (ROSE) results of each maneuver from which a specimen was obtained. Specimens must be documented & associated with the specific maneuver/specific device from which they were obtained. • Final Cytology Report(s)	Scanned de-identified file for upload in eCRF
Operative Note(s)	Remain on-site
Discharge X-Ray Report	Scanned de-identified file for upload in eCRF
Procedure-related SAE Discharge Summaries	Scanned de-identified file for fax or email transmission the BSC Safety Trial Manager

Abbreviations:

9. Statistical Considerations

9.1. Endpoints

9.1.1. Primary Endpoint

Clinical success is defined as the iNod System's ability to acquire adequate specimens of cellular matter suitable for the cytologic evaluation of targeted lung lesions, under real-time visualization. The rate of Clinical Success will be calculated as the number of peripheral pulmonary lesions for which adequate cytologic specimens suitable for cytologic evaluation were obtained divided by the number of lesions the iNod System was attempted.

Hypotheses

There will be no formal statistical hypothesis tested since this is an observational study documenting the first human use of the iNod System

Sample Size

Enrollment is capped at 30 subjects with a maximum of 10 subjects per center. Since no formal hypothesis will be tested, there is no statistical justification of sample size.

Peripheral pulmonary lesions vary in their location in the tracheobronchial tree. Their size, characteristics (e.g., concentric vs. eccentric), and a sample size of 5-10 subjects per site allows greater potential to evaluate the usability and performance of the system for visualization and sampling this range of lesions.

Performance feedback for this traditional feasibility study is sought from more than 1 physician. While staying within the sample size confines of a traditional feasibility study, Boston Scientific has elected to seek the expertise of 2 to 3 interventional bronchoscopists.

Statistical Methods

Since no formal hypothesis is tested, only descriptive statistics will be used to summarize the primary endpoint.

9.2. General Statistical Methods

9.2.1. Analysis Sets

Intent-to-Treat Cohort

The intent-to-treat (ITT) cohort consists of subjects enrolled in the study regardless of whether a specimen was obtained from the iNod System.

Per Protocol Cohort

The per-protocol (PP) cohort is a subset of the ITT subjects for whom a specimen was obtained using the iNod System.

9.2.2. Control of Systematic Error/Bias

All subjects who have met the inclusion/exclusion criteria and have signed the ICF will be eligible for enrollment in the study. Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database

9.2.3. Number of Subjects per Investigative Site

A maximum of 10 subjects can be enrolled at each investigative site.

9.3. Data Analyses

Descriptive statistics will be presented for all ITT and PP subjects. The mean (± standard deviation) will be used to describe continuous variables with a normal distribution and the median (and interquartile range) will be used to describe continuous variables with a

skewed distribution. Frequency tables will be used to summarize discrete variables. Proportions of subjects with adverse events and SAEs will be reported.

9.3.1. Interim Analyses

No formal interim analyses are planned for the purpose of stopping this study early. Informal interim analysis may be conducted for the purpose of submissions of abstracts to major professional meetings.

9.3.2. Subgroup Analyses

There are no planned subgroup analyses.]

9.3.3. Justification of Pooling

The analyses will be presented using data pooled across centers as well as by center for the primary endpoint. If deemed appropriate, stratified and multivariate analysis techniques, including Chi-square test or logistic regression will be used to assess differences between study centers to justify pooling data across centers.

9.3.4. Changes to Planned Analyses

Any changes to the planned statistical analyses will be documented in an amended Statistical Analysis Plan approved prior to performing the analysis. Changes from the planned statistical methods after performing the analysis will be documented in the clinical study report along with a reason for the deviation.

10. Data Management

10.1. Data Collection, Processing, and Review

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata. All changes made to the clinical data will be captured in an electronic audit trail and available for review by Boston Scientific Corporation (BSC) or its representative. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to

data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

10.2. Data Retention

The Investigator or Investigational site will maintain, at the investigative site, in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change.

11. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation.

12. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using entry onto the eCRF. Sites may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, center re-training, or discontinuation) will be put into place by the sponsor.

13. Device/Equipment Accountability

The investigational devices/equipment shall be securely maintained, controlled, and used only in this clinical study.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal.

Records shall be kept by study personnel to document the physical location and conditions of storage of all investigational devices/equipment.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices/equipment, which shall include the following

- Date of receipt
- Identification of each investigational device/piece of equipment (batch number or unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Date on which the investigational device/piece of equipment was returned/explanted from subject, if applicable
- Date of return of unused, expired, or malfunctioning investigational devices/equipment, if applicable.

Written procedures may be required by national regulations.

14. Compliance

14.1. Statement of Compliance

This study will be conducted in accordance with relevant sections of the International Standard (ISO) 14155: Clinical Investigation of Medical devices for Human Subjects – Good Clinical Practice, the relevant parts of the ICH Guidelines for Good Clinical Practices, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the

required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

14.2. Investigator Responsibilities

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational plan/protocol, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency.
- Report to BSC, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.

- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

14.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

14.3. Institutional Review Board

Prior to gaining Approval-to-Enroll status, the investigational center will provide to the sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the Investigator's reports and the IRB/EC continuance of approval must be provided to the sponsor.

14.4. Sponsor Responsibilities

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Boston Scientific will keep subjects' health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects;

subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

14.4.1. Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during the iNod System procedure required by the protocol. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices.

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the HCP
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

14.5. Insurance

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

15. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

16. Potential Risks and Benefits

16.1. Anticipated Device-related & Procedure-related Adverse Events

The following anticipated adverse events (AE) have been identified with the diagnostic procedure that is being studied. Anticipated Adverse Events related specifically to the device (iNod System) as well as similar standard of care procedural devices are identified with an asterisk (*).

- Allergic Reaction to Medication
- Aspiration
- Bleeding*
- Bronchospasm
- Cardiac Arrhythmia or Arrest
- Cough
- Dyspnea
- Fever
- Infection
- Hemomediastinum*
- Hemorrhage*
- Hypotension
- Infection*
- Inflammation*
- Laceration*
- Laryngospasm
- Nausea
- Nerve Damage
- Over sedation leading to:
  - Hypercapnia
  - Hypoxemia
  - Hypotension
- Pain
- Perforation*
- Post-Procedural Chest Pain
- Post-Procedural Hiccup
- Pneumonia
- Pneumoperitoneum*

- Pneumothorax *
- Pneumomediastinum*
- Respiratory Depression or Arrest
- Tissue Damage*
- Tumor Seeding
- Transient Lowered Oxygen
- Vomiting

16.2. Risks Associated with the Study Device(s)

No incremental risks are associated with the study device that are above those of market available products.

16.3. Risks associated with Participation in the Clinical Study

Participation in the trial may result in a prolonged procedure when compared to standard of care sampling of peripheral pulmonarylesions.

Pariticipation in the trial may result in an unintended breach of the subject's confidentiality.

16.4. Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

16.5. Anticipated Benefits

Subjects may not receive any benefit from being in this study. However, medical science and future subjects may benefit from this study.

16.6. Risk to Benefit Rationale

Based on collected reports in literature to-date, the risk-to-benefit ratio is within reason for foreseeable risks. However, literature reports do not always capture all side effects. Observation and follow-up of subjects is required as outlined in the protocol.

17. Safety Reporting

17.1. Reportable Events by Investigational Site to Boston Scientific

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- All Serious Adverse Events
- All Study Device, Study Procedure, and Study Procedure Anesthesia-related Adverse Events
- All Investigational Device Deficiencies
- Unanticipated Adverse Device Effects
- New findings/updates in relation to already reported events

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device, procedure, or anesthesia, it should be submitted as an adverse event and/or device deficiency.

Any AE event required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases are not reported as AEs unless there is an increase in severity of frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of one (1) specific SAE (see Table 17.2-1 for AE definitions).

Refer to Section 16 for the known risks associated with the study device(s).

Adverse event definitions are provided in Table 17.1-1. Administrative edits were made to combine definitions from ISO 14155-2011 and MEDDEV 2.7/3 12/2010.

Table 17.1-1: Safety Reporting Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved (any procedure in the clinical investigation plan).

Table 17.1-1: Safety Reporting Definitions

Term	Definition
	NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use, the deployment, the implantation, the installation, the 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.
Serious Adverse Event (SAE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolonged hospitalization of existing hospitalization, or o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1**: 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.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812* **Note**: For US IDE studies only, otherwise remove UADE from table	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Device Deficiency *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

Table 17.1-1: Safety Reporting Definitions

Term	Definition

Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of a specific SAE (see Table 17.1-1 for AE definitions).

Any related AE experienced by the study subject after informed consent, whether during or subsequent to the procedure, must be recorded in the eCRF.

Refer to Section 16 for the known risks associated with the study device(s).

17.2. Relationship to Study Device(s)

The Investigator must assess the relationship of the AE to the study device, study procedure, or study procedure anesthesia as related or not related. See criteria in Table 17.2-1:

Table 17.2-1: Criteria for Assessing Relationship of Study Device, Study Procedure, & Study Procedure Anesthesia to Adverse Event

Classification	Description
Not Related	The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.
Related	• The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product, or • There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or • There is no other reasonable medical explanation for the event.

17.3. Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in Table 17.3-1.

Table 17.3-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Unanticipated Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study

Table 17.3-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Serious Adverse Event including Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event	• When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency 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 is considered a reportable event.	Complete Device Event Form	• Within 2 business days of first becoming aware of the event and as per local/regional regulations. • Reporting required through the end of the study
Adverse Event	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g. Recommend within 10 business days) after becoming aware of the information • Reporting required through the end of the study

Abbreviations: AE=adverse event; CRF=case report form; IDE=Investigational Device Exemption; UADE=unanticipated adverse device effect

17.4. Boston Scientific Device Deficiencies

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are to be reported as Device Events and are not to be reported as

adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded on the Adverse Event eCRF.

Any Investigational Device Deficiency 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 is considered a reportable event.

17.5. Reporting to Regulatory Authorities / IRBs / ECs / Investigators

BSC is responsible for reporting adverse event information to all participating investigators and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of UADE and SAE as required by local/regional regulations.

18. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be approved by BSC or it's delegate (e.g. CRO), the center's IRB/EC, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative center's IRB/EC. Any modification requires approval from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the center in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,

- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the center and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC. The new version of the ICF must be approved by the IRB/EC. Boston Scientific approval is required if changes to the revised ICF are requested by the center's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

19. Safety Monitoring Process

To promote early detection of safety issues, the BSC Medical Monitor will provide evaluations of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. This is expedited through BSC's Global Safety Office, which is responsible for coordinating the collection of information for the subject dossier from the centers and core laboratories. During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document information.

20. Suspension or Termination

20.1. Premature Termination of the Study

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

20.1.1. Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

20.2. Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval

Any investigator or IRB in the iNod Feasibility Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated IRBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

20.3 Requirements for Documentation and Subject Follow-up

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating centers by Boston Scientific. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event an investigator terminates participation in the study, study responsibility will be transferred to a co-investigator, if possible. In the event there are no opportunities to

transfer investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The investigator must return all documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

20.4 Criteria for Suspending/Terminating a Study Center

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled for a period beyond 3months after center initiation, or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the center will continue to be followed through resolution of any procedure-related adverse events unled they are considered to endure in a chronic nature. The Principal Investigator at the center must make provision for these follow-up visits unless BSC notifies the investigational center otherwise.

21. Publication Policy

In accordance with the Corporate Policy on the Conduct of Human Subject Research, BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. In accordance with the Corporate Policy for the Conduct of Human Subject Research, BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

1. All authorship and contributorship requirements as described above must be followed.
2. BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.

3. The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

22. Bibliography

1. World Health Organization. International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevelence Worldiwde in 2012. Lung Cancer. Accessed November 10, 2014.
2. Centers for Disease Control and Prevention. National Center for Health Statistics. CDC WONDER On-line database, compiled from compressed Mortaility File 1999-2012 Series 20 No. 2R, 2014.
3. U.S. Nation Institues of Health. National Cancer Institute. SEER Cnacer Statistics Review, 1975-2011.
4. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143:e93S-120S.
5. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. The New England journal of medicine 2011; 365:395-409.
6. Wahidi MM, Govert JA, Goudar RK, et al. Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007; 132:94S-107S.
7. Gaeta M, Pandolfo I, Volta S, et al. Bronchus sign on CT in peripheral carcinoma of the lung: value in predicting results of transbronchial biopsy. AJR Am J Roentgenol 1991; 157:1181-1185.
8. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143:e142S-165S.
9. Eberhardt R, Morgan RK, Ernst A, Beyer T, Herth FJF. Comparison of suction catheter versus forceps biopsy for sampling of solitary pulmonary nodules guided by electromagnetic navigational bronchoscopy. Respiration 2010;79(1):54-60.
10. Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. Chest 2012;142(2):385-393.
11. Goldstein RA, et al. Clinical role of bronchoalveolar lavage in adults with pulmonary disease. Am Rev Respir Dis. 1990 Aug;142(2):481-6.

23. Abbreviations and Definitions

23.1 Abbreviations

Abbreviations are shown in table 23.1-1.

Table 23.1-1: Abbreviations

Acronym	Definition
ADE	Adverse Device Effect
AE	Adverse Event
CT	Computed Tomography
CXR	Chest X-Ray
DFU	Directions for Use
EBB	Endobronchial Biopsy
EBUS	Endobronchial Ultrasound
eCRF	Electronic Case Report Form
EC	Ethics Committe
EDC	Electronic Data Capture
FB	Flexible Bronchoscopy
FDA	Food and Drug Administration
GCP	Good Clinical Practices
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutonal Review Board
ISO	International Standards Organization
ITT	Intent-to-Treat
MDU	Motor Drive Unit
PP	Per-Protocol
PZT	Piezoelectric Transducer
R-EBUS	Radial Endobronchial Ultrasound
ROSE	Rapid On-Site Evaluation
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TBLB	Transbronchial Lung Biopsy
TBNA	Transbronchial Needle Aspiration
TTNA	Transthoracic Needle Aspiration
VATS	Video-Assisted Thorascopic Surgery
VB	Virtual Bronchoscopy

23.2. Definitions

Terms are defined in Table 23.2-1.

Table 23.2-1: Definitions

Term	Definition
SOURCE DATA	All information in original records and certified copies of original records of clinical finding, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in the source documents (original records or certified copies).
SOURCE DOCUMENTS	Original documents, data, and records.

Abbreviations are defined in Table 23.1-1.