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

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Statistical Analysis Plan

Clinical Investigation Plan Title	A post-market feasibility study evaluating location accuracy using the superDimension™ Navigation System Version 7.2 with Fluoroscopic Navigation Technology in subjects undergoing lung lesion biopsy
Clinical Investigation Plan Identifier	MDT18004ILSFNV
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[redacted]

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• New Document	Yun Bai, Statistician
1.1	• Revise the "Figure 1. Procedure Steps"	Yun Bai, Statistician
1.2	• Revise "Figure 1" and the secondary endpoint	Yun Bai, Statistician

2. List of Abbreviations and Definitions of Terms

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

Abbreviation	Definition
MDR	medical device reporting
ROSE	rapid on-site evaluation
SAE	serious adverse event
SAP	statistical analysis plan

3. Introduction

This is a post-market feasibility study evaluating location accuracy using the superDimension™ Navigation System Version 7.2 with Fluoroscopic Navigation Technology in subjects undergoing lung lesion biopsy.

This document provides a detailed description of the statistical methods and procedures to be implemented during the analysis of the study.

This statistical analysis plan (SAP) is based on the CIP version 1.0 dated on 09APR2018.

4. Study Objectives

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

5. Investigation Plan

This post-market feasibility study is planned in up to 50 subjects meeting the inclusion criteria and undergoing elective ENB with the superDimension™ Navigation System v7.2 with Fluoroscopic Navigation Technology. The study will confirm the location accuracy of the optional local registration feature. Enrolled subjects will first undergo a standard ENB procedure to navigate to within 2.5 cm of the target lesion. Local registration with Fluoroscopic Navigation Technology will be conducted and fluoroscopy and CBCT scans will be used to document that the biopsy tool location accuracy. Periprocedural endpoints include confirmation of accurate positioning of the virtual target (representing the target lesion), technical success, relational accuracy, adequate periprocedural location, procedure time, adequacy of tissue captures for pathology, tool usage, and histopathological results. Safety will be evaluated immediately post-procedure and 4-7 days post-procedure.

This study will be conducted in subjects over the age of 18 undergoing elective biopsy of lung lesions greater than 10 mm in diameter. Additional inclusion/exclusion criteria are listed in CIP section 8.3 and 8.4.

The overview of procedure (Figure 1):

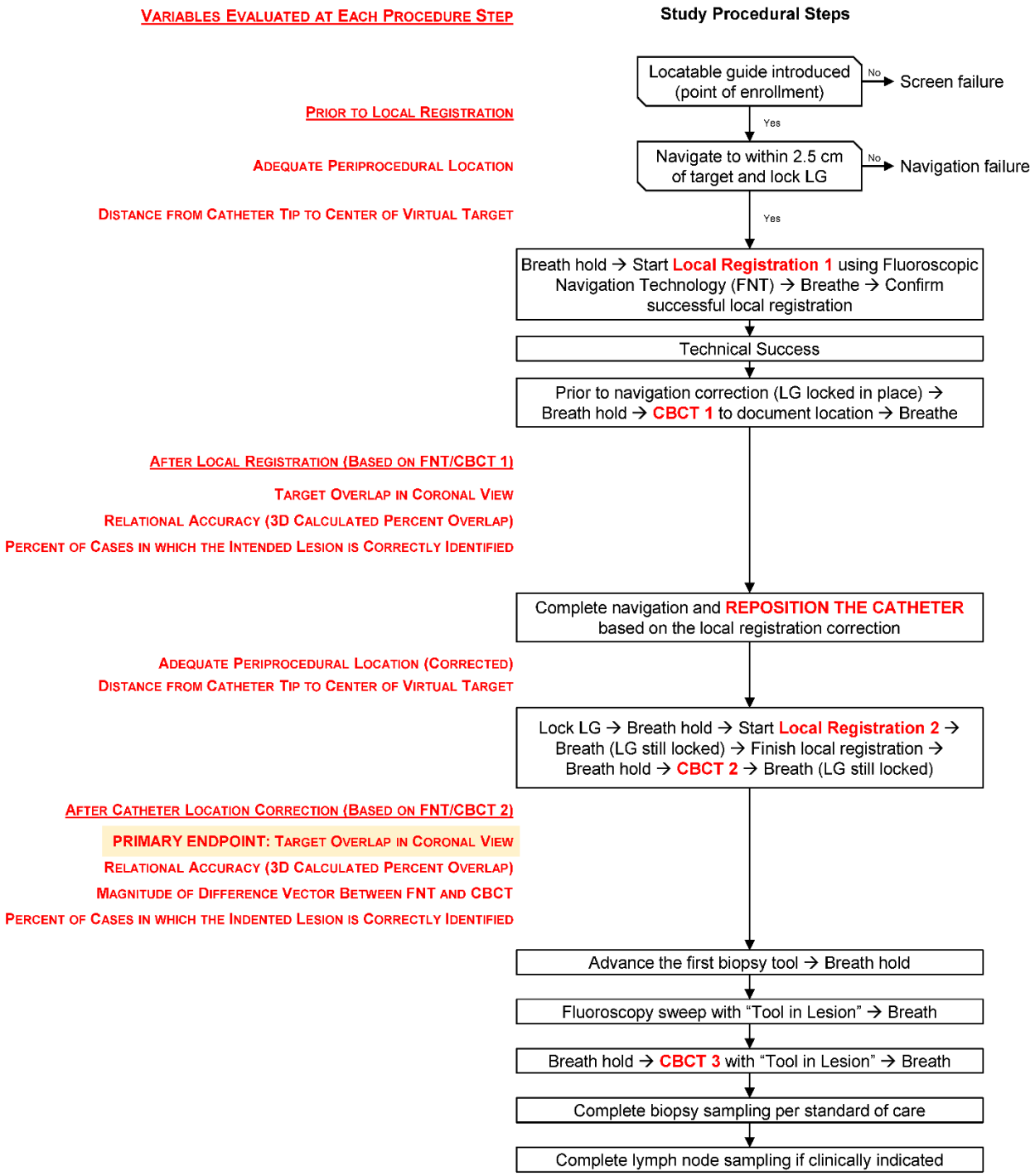

Figure 1. Procedure Steps

6. Determination of Sample Size

This study will enroll up to 50 subjects meeting the inclusion criteria, with a maximum of 25 subjects per site. The sample size of this feasibility study is not based on power calculations of a statistical hypothesis test.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

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

Table 1. Schedule of Events

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

Subject disposition (e.g., number of subjects enrolled, number of subjects completing the study) will be summarized with frequency tables.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Deviations are instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP. All deviations must be documented and explained, regardless of the reason for the deviation.

The total number of protocol deviations and total number of subjects with deviations will be provided by deviation type for all enrolled subjects. Number of protocol deviations and number of subjects with deviations by each investigational site will also be provided.

7.1.3 Analysis Sets

- Enrolled subjects

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

- Technically Successful cases

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

The following study endpoints will be evaluated in Technically Successful cases:

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

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

7.2 General Methodology

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

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

7.3 Center Pooling

This is a multi-center clinical study, with standardization of subject enrollment, data entry and adverse event reporting. All the data will be pooled for reporting.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

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

7.5 Adjustments for Multiple Comparisons

No multiple comparisons/multiplicity adjustments will be made.

7.6 Demographic and Other Baseline Characteristics

Baseline, demographic and medical history data will be collected for all enrolled participants. These characteristics will be summarized using descriptive statistics.

7.7 Treatment Characteristics

- Procedure Characteristics

  The subject-based procedure characteristics will be summarized using descriptive statistics.

- Lesion Characteristics

  The lesion-based characteristics will be summarized using descriptive statistics.

7.8 Evaluation of Objectives

7.8.1 Primary Endpoint

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

The primary endpoint will be evaluated in Technically Successful cases (local registration complete) and calculated as the number and percentage of cases in which the center of the virtual target was correctly placed to overlap the target lesion in coronal view, as confirmed by CBCT. In 'MUO_IMAG' CRF, the subject meets the primary endpoint if 'Target Overlap in Coronal View' is checked 'Yes'.

7.8.2 Secondary Endpoints

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

- Number of cases that are technically successful (successful completion of local registration), define as,
  - In 'LESN_CHAR' CRF

    The technically successful is defined as that 'Was local registration successful' is checked 'YES'. The results will be summarized using frequency measures in the format of p% (x/N), with x being the number of lesions with successful completion of local registration and N being the number of lesions undergo the procedure.

- In cases that are not technically successful, reason for incomplete local registration in each target lesion, define as,
  - In 'LESN_CHAR' CRF

    If 'Was local registration successful' is checked 'NO', list all detail from 'If No, provide reason'.

- Investigator confirmation that the catheter is in an "Adequate Periprocedural Location" (the location of the extended working channel with the proceduralist makes the decision that placement is adequate and clinically acceptable to proceed with tissue sampling), define as,
  - In 'LESN_CHAR' CRF

    If 'Adequate Periprocedural Location' is checked 'YES'. The results will be summarized using frequency measures in the format of p% (x/N), with N being the number of lesions undergo the procedure.

- Total procedure time, define as,

  In 'PROC' CRF, first entry of the bronchoscope to the last exit of the bronchoscope

- ENB procedure time, define as,

  In 'PROC' CRF, total time from the first entry of the extended working channel or locatable guide until the last exit of the extended working channel.

- Total fluoroscopy time, as measured by the fluoroscopy system, define as,

  In 'PROC' CRF, 'What was the total fluoroscopic time' will be summarized using the descriptive statistics.

- Adequacy of the ENB-aided tissue sample for rapid on-site evaluation (ROSE) of cytologic samples by pathology (when applicable)

  In 'DIAG' CRF, if 'ROSE Diagnosis' is not checked 'INADEQUATE TISSUE FOR ROSE'.

- Histopathological call based on ROSE of the ENB-aided tissue sample (when applicable)

  In 'DIAG' CRF, 'ROSE Diagnosis' will be summarized using the descriptive statistics of categorical variables.

- Final pathology results of the ENB-aided tissue sample

  In 'DIAG' CRF, 'Pathology Diagnosis' will be summarized using the descriptive statistics of categorical variables.

- Biopsy tools used, tool order, number of passes, and final pathology of the ENB-aided sample

  In 'DIAG' CRF, 'Tool Name', 'Tool Order' and 'Number of Passes' will be summarized using the descriptive statistics or data listing.

In Technically Successful cases (local registration complete):

- Percentage of cases in which the intended lesion is correctly identified (as opposed to a nontarget lesion or normal lung tissue) as indicated by the system software.

  In MUO CRFs, 'Was the target/planned lesion correctly marked by the physician?' will be summarized using the descriptive statistics to present the count and percentage.

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

  Relational accuracy, defined per protocol as the three-dimensional relationship between the catheter and the lesion in terms of distance and vector, was calculated as the three-dimensional percentage overlap between the virtual target and the actual lesion in CBCT.

  In MUO CRFs, 'Calculated Percent Overlap' will be summarized using descriptive statistics.

7.9 Safety Evaluation

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

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

In addition to the Safety Endpoints described above, all Adverse Events related to the superDimension™ navigation system, associated tools, or ENB procedure as described in CIP Section 11 will be collected for all enrolled subjects. Summary of overall event, events relatedness, seriousness and severity will be provided. To assess safety, the number and percentage of subjects with adverse events will be summarized and the number of events will be provided for each category as well.

7.10 Health Outcomes Analyses

N/A

7.11 Changes to Planned Analysis

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

8. Validation Requirements

Level II: The peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.