Author: Sander Langereis
PEPF: Clinical Operations Clinical Research Associate (CRA)

Sponsor: Philips Medical Systems Nederland BV
Veenpluis 6
5684 PC Best
The Netherlands

Department: Philips IGT-S Clinical Science & Medical Affairs.

Protocol version and date: Revision 04 (2024-June-19)

Approval

Name	Role	Date	(Electronic) Signature
Kevin Najarian	PEPF: Biostatistician		
Pim van Lochem	PEPF: Clinical Development		
Joris de Groot	Clinical Operations Lead		
Yesheshvi Anush Puvvada	Regulatory Affairs Officer		

Controlled Document is approved when all approvers have signed. Approval and effective date are the dates of the latest signature.

Revision History

Revision	Revision Date	Author	Changes/Comments
00	2022-Nov-22	Sander Langereis	Initial version
01	2022-Dec-14	Sander Langereis	(Cross-)references issues fixed IFU revision updated
02	2023-June-02	Sander Langereis	Update of: study timelines, wording on safety reporting, references IFU and IB, Risks and benefits, table of anticipated adverse device effects
03	2023-Jul-11	Sander Langereis	Clarification major protocol deviations section 8.1
04	2024-Jun-19	Sander Langereis	Increase sample size, IFU revision updated due to iteration device, administrative change to address error in description intra-procedural study practice

Open Issues

None

Table of Contents

1. Document Introduction

1.1. Purpose

This document describes the minimum amount of information to be included in the feasibility clinical investigation protocol based on the regulations to ensure safety and well-being of human subjects and users.

1.2. Scope

The AirWaze investigational device (version 1.1, Philips Medical Systems), hereafter referred to as AirWaze, has been designed to reduce the cognitive load and therewith overall procedural accuracy of CBCT guided navigation bronchoscopy (NB) for lung interventions. The main goal of the AirWaze prototype is to improve the ease-of-use of CBCT-guided NB to help improve widespread implementation and overall accuracy of this novel technology for minimally-invasive lung interventions. This widespread implementation of CBCT guided NB is necessary for coping with the increasing number of patients with pulmonary lesions suspicious of malignancy.

The software tools of the AirWaze investigational device (version 1.1) have an improved user interface compared to a previously clinically evaluated AirWaze prototype (version 1.0) which now consists of a procedural planning module, an image-guided navigation module with augmented fluoroscopy, and dedicated low dose radiation imaging protocols for tool-in-lesion confirmation. Benefits may include a reduction in the procedure time, less radiation exposure for the patient, and less cognitive load for the physicians during navigation bronchoscopy, while maintaining patient safety and a high diagnostic accuracy for peripheral pulmonary nodules.

The clinical investigation protocol (CIP) is aimed to assess the clinical and technical feasibility of the AirWaze tools for CBCT-guided lung interventions. This feasibility clinical investigation protocol applies to study: “AirWaze – easy and advanced tools for CBCT-guided lung interventions”.

1.3. References

Reference	Identification	Title / additional remarks
[REF-1]	XCY607-131101_rev02	Investigator Brochure AirWaze
[REF-2]	XCY607-131132_r03	Instructions for Use (IFU) AirWaze clinical

1.4. Definitions & Abbreviations

Term	Description
ADE	Adverse Device Effect
AE	Adverse Event
AF	Augmented Fluoroscopy
ASA	American Society of Anesthesiologists
CA	Competent Authority
CBCT	Cone-Beam Computed Tomography
CBCT-FS	Cone-Beam Computed Tomography-FluoroSweep
CE	Conformité Européenne (European Conformity)
CFR	Code of Federal Regulation
CL	Confidence Level
(e-)CRF	(Electronic) Case Report Form
CIP	Clinical Investigation Protocol
CRO	Contract Research Organization
DAP	Dose Area Product
(r-)EBUS	(radial-)Endobronchial Ultrasound
ENB	Electromagnetic Navigation Bronchoscopy
EU	European Union
EU-MDR	Medical Device Regulation (EU) 2017/745 of the European Parliament

Term	Description
FDA	Food Drug Administration
FS	FluoroSweep
HCP	Health Care Professional
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
MEC	Medical Ethic Committee
OR	Operating Room
PoC	Proof-of-Concept
PPN	Peripheral Pulmonary Nodule
NOACs	Novel Oral Anticoagulants
NB	Navigation Bronchoscopy
RAB	Robot assisted bronchoscopy
ROSE	Rapid on-site evaluation
SAE	Serious Adverse Event
SURG-TLX	Surgical Task-load Index
SUS	System Usability Scale
TLCA	Tool-in-lesion confirmation accuracy
TSM	touch-screen module
TTNA	transthoracic needle aspiration
UMC	University Medical Centre
USADE	Unanticipated Serious Adverse Device Effect

2. Summary

Identification of investigational device

The AirWaze investigational device (version 1.1, Philips Medical Systems, The Netherlands) has been developed for CBCT-guided bronchoscopic interventions in order to reduce the operator's cognitive load and therewith improve the overall accuracy for Cone-Beam Computed Tomography (CBCT)-guided navigation bronchoscopy (NB) procedures. The AirWaze software tools are designed to facilitate the physician to plan the envisioned pathway to the target lesion, to navigate devices to the target lesion under image-guidance, and to confirm tool-in-lesion positioning for subsequent interventions.

The AirWaze investigational device (version 1.1) consists of the following features:

1. Advanced planning software that supports bronchoscopists in optimally preparing the NB procedure by reconstructing the patient-specific airways, proposed navigation trajectory and target lesion in 3D from a pre-procedural CT scan;
2. Augmented fluoroscopy based upon an intra-procedurally acquired CBCT that provides in-room image-guided, real-time navigation by augmenting the fluoroscopy imaging with an overlay of the airways, proposed navigation trajectory, and target lesion;
3. Automatic device detection that visualizes the endobronchial catheter and lesion to support device-in-lesion assessment;
4. Directional guidance software that provides guidance for accurate device navigation, positioning, and device-in-lesion confirmation;
5. CBCT-FluoroSweep, a dedicated low dose radiation protocol, that supports pulmonologists in acquiring lower radiation dose tool-in-lesion confirmation scans instead of the conventionally performed CBCT scan.

Study design

This is a prospective, single center, feasibility clinical investigation at the Radboud University Medical Centre that is sponsored by Philips Medical Systems (Best, The Netherlands). This study involves the assessment of the system usability of the AirWaze investigational device and the accuracy of the tool-in-lesion confirmation scan CBCT-FluoroSweep compared to the conventional CBCT.

Objectives

Primary objective

The primary objectives of this feasibility clinical investigation are to assess the overall usability of the Philips AirWaze investigational device as measured by the System Usability Score (SUS), and the accuracy of the tool-in-lesion confirmation scan CBCT-FluoroSweep compared to the conventional CBCT.

Secondary objectives

The secondary objectives of this feasibility clinical investigation are:

- To assess intuitiveness of the individual AirWaze features by the physicians.
- To assess performance of the following algorithms:
  a) Segmentation of the bronchial tree on pre-procedural CT.
  b) Elastic registration of the intraoperative CBCT scans with preprocedural CT scan.
  c) Automatic device detection on intraoperative CBCT scans.

- To assess the quality of the interventional plan (pre-procedural planning).
- To assess the confidence levels of interventional pulmonologists while using AirWaze (pre-procedural planning).
- To assess the intraprocedural cognitive load of CBCT-guided NB.
- To determine the radiation exposure for patients and staff.
- Report all adverse events, adverse device effects and device deficiencies.

Endpoints

Primary endpoint

- System Usability Score (SUS) of AirWaze investigational device.
- Accuracy of the tool-in-lesion confirmation scan CBCT-FS compared to the conventional CBCT (gold-standard) based on tool-in-lesion definitions and usefulness of the scans to guide to the lesion.

Secondary endpoints

The secondary endpoints of this clinical feasibility investigation are:

- Semi-structured questionnaires to assess intuitiveness of AirWaze features for CBCT-guided biopsy of peripheral pulmonary nodules.
- Quantitative and qualitative assessment of developed algorithms:
  a) Segmentation bronchial tree on pre-procedural CT.
  b) Elastic registration of the intraoperative CBCT scans with preprocedural CT scan.
  c) Automatic device detection on intraoperative CBCT scans.
- The quality of the interventional planning utilizing the AirWaze planning software assessed by semi-structured questionnaires.
- Confidence levels of pulmonologists regarding: (i) the localization of the lesion and planned navigation trajectory; (ii) reaching the first pulmonary lesion based on the planning assessed by semi-structured questionnaires.
- The cognitive load of pulmonologists during CBCT-guided navigation to the first pulmonary lesion assessed by semi-structured questionnaires.
- Radiation exposure for patients and staff.
- Adverse events, adverse device effects and device deficiencies.

Main inclusion criteria

In order to be eligible to participate in this study, a subject must meet the following criteria:

- Age 18 years or older at the time of informed consent.
- ASA physical status between 1 and 3.
- Subject is willing and able to give written informed consent for clinical investigation participation prior to the procedure.
- Subject has a pulmonary lesion with an indication for diagnostic evaluation following current clinical guidelines and/or as decided by multi-disciplinary team consultation.
- Suitable for CBCT-guided endobronchial nodule biopsy under general anaesthesia.
- Pre-procedural (PET-)CT scan is available prior to the CBCT-NB intervention.

Main exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Aged 17 or younger at the time of informed consent.
- ASA physical status is equal to and greater than 4.
- Not willing or not able to give informed consent.
- Does not indicate diagnostic evaluation with navigation bronchoscopy.
- Not suitable for CBCT-guided endobronchial nodule biopsy via navigation bronchoscopy under general anaesthesia.
- There is no recent pre-procedural (PET-)CT scan available.
- Known bleeding disorders.
- Contra-indication for temporary interruption of the use of anticoagulant therapy, such as acenocoumarol, warfarin, therapeutic dose of low molecular weight heparins, clopidogrel, or analogues, NOACs).
- Known allergy for lidocaine or other allergies interfering with the procedure.
- Uncontrolled pulmonary hypertension.
- Recent and/or uncontrolled cardiac disease.

- Compromised upper airway (*e.g.* concomitant head and neck cancer or central airway stenosis for any reason such that endobronchial access is considered unsafe).
- Potentially confounding drug or device trial during the clinical study. Co-enrollment in concurrent trials may be allowed provided pre-approval is obtained from the Philips Clinical Study Manager.
- All vulnerable subjects, such as immune-compromised subjects, subjects lacking the capacity to provide consent, patients in emergencies, pregnant or breastfeeding women, or any other subject who meets exclusion criteria, according to applicable national laws, if any.
- Woman of childbearing potential who is known to be pregnant on admission.
- Any condition that in the judgment of the investigator could impose hazards to the patient if study therapy is initiated or affect the participation of the subject in the study.
- Subject is Philips employee or their family members residing with this Philips employee.

No. of subjects

A total of 37 patients will be included in this feasibility study.

Taking into account a 10% drop-out rate, it is expected by experts that a Per Protocol population of 33 patients is to collect sufficient data for the evaluation of the primary and secondary objectives and to de-risk the AirWaze features.

Operators

In the pre-procedural evaluation of the AirWaze software device, at least three users (n=3) (*e.g.* interventional pulmonologist experts) will be performing the pre-procedural planning of the CBCT guided peripheral pulmonary nodules biopsies. In the peri-procedural evaluation of the AirWaze software device, at least three certified bronchoscopists (n=3) (*e.g.* interventional pulmonologist experts) will be performing CBCT guided biopsies of peripheral pulmonary nodules biopsies.

Study procedures

Current clinical practice

- Pre-procedural

In current clinical practice, the lesion identification and trajectory planning are performed by interventional pulmonologists who need to mentally reconstruct the navigation trajectory (mind-map) based on the available CT-images in routine DICOM viewers.

- Intra-procedural

The procedure starts with an inspection bronchoscopy to examine the trachea and proximal airways. If the tumour is not visible endobronchially, navigation bronchoscopy is continued by advancing a pre-formed curvature catheter through the bronchoscope under image guidance. Advanced imaging with CBCT and AF will expedite catheter guidance through the airways. The CBCT gives feedback about the position of the catheter in a three-dimensional space. Once tool-in-lesion is confirmed with either radial-endobronchial ultrasound (rEBUS), rapid on-site evaluation (ROSE) and/or CBCT, tissue sampling is performed. If indicated, an EBUS is performed for staging lung cancer.

Study practice

- Pre-procedural

In this study, pre-procedural planning will be performed with Philips' AirWaze software. The CT-scan is loaded into the software system and the airways will be segmented and visualized. The target lesion is segmented with a one-click segmentation by the physician and is followed by a selection of the pathway to the target lesion.

- Intra-procedural

As performed routinely, an inspection bronchoscopy is performed at the start of the procedure. The selected pathway to the target lesion from the planning will be registered to and overlayed on the first performed CBCT. This overlay is visible at any time and will help the physician guide to the target lesion. If CBCT is indicated in conventional procedures, a low-dose CBCT-FluoroSweep (CBCT-FS) scan will be performed of the same catheter and tool position. The CBCT-FS has the same function as the regular CBCT, but it will

be evaluated whether the low-dose CBCT-FS is as accurate as the CBCT. Once tool-in-lesion is confirmed with either rEBUS, ROSE and/or CBCT-FluoroSweep (with regular CBCT as gold standard), tissue sampling is performed. If indicated, an EBUS is performed for staging lung cancer.

Follow-up

Subjects are enrolled in the clinical investigation for the duration of the interventional procedure until 1 week post-procedure. A safety follow-up visit will take place at 1 week post-procedure.

Duration of the study

The total duration of the study is expected to take approximately 18 months, from the first patient to the last patient (excluding reporting). The first patient was enrolled in October 2023.

3. Device Description

3.1. Summary description of the investigational device

The AirWaze Investigational Device (version 1.1) is developed by Philips Medical Systems, and hereinafter referred to as AirWaze. The investigational software device consists of five main features (*Figure 1*):

1. Advanced planning software that supports bronchoscopists in optimally preparing the navigation bronchoscopy (NB) procedure by reconstructing the patient-specific airways, proposed navigation trajectory and target lesion in 3D from a pre-procedural CT scan;
2. Augmented fluoroscopy based upon an intra-procedurally acquired CBCT that provides in-room image-guided, real-time navigation by augmenting the fluoroscopy imaging with an overlay of the airways, proposed navigation trajectory, and target lesion;
3. Automatic device detection that visualizes the endobronchial catheter and lesion to support device-in-lesion assessment;
4. Directional guidance software that provides guidance for accurate device navigation, positioning, and tool-in-lesion confirmation;
5. CBCT-FluoroSweep, a dedicated low dose radiation protocol, that supports pulmonologists in acquiring lower radiation dose tool-in-lesion confirmation scans instead of the conventionally performed CBCT scan.

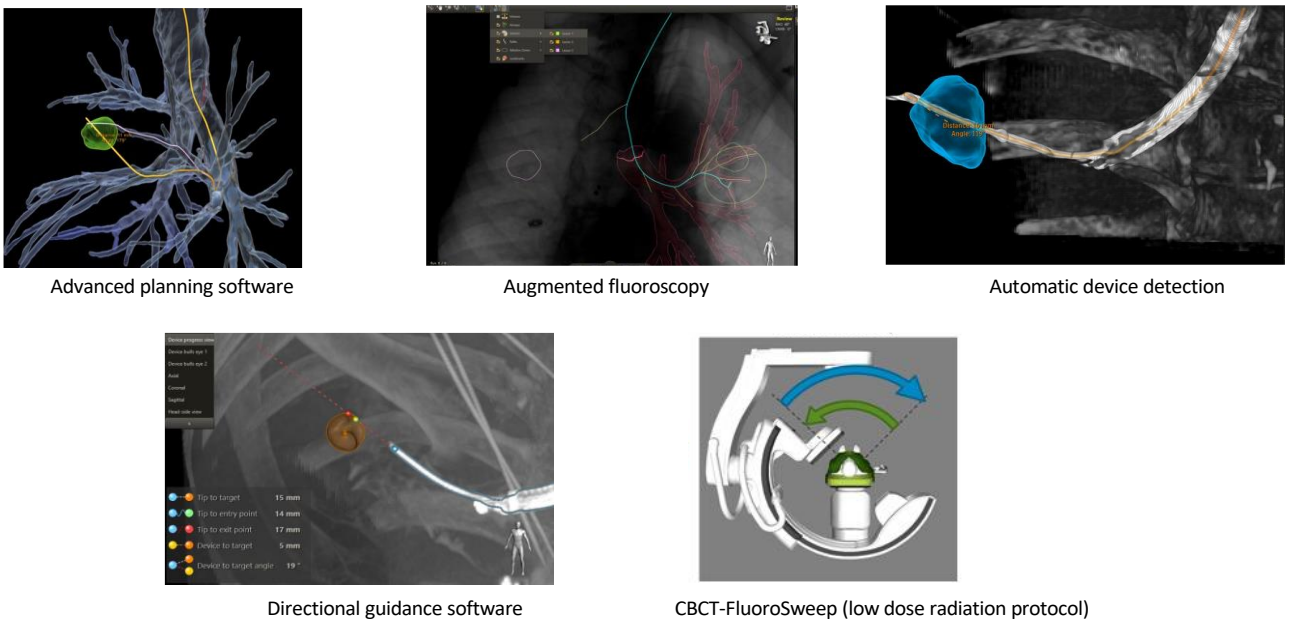

Figure 1. Software features of the AirWaze investigational device (version 1.1), namely advanced planning software (top left), augmented fluoroscopy (top middle), automatic device detection (top right), directional guidance software (bottom left), and CBCT-FS imaging protocols (bottom right).

Table 1. Overview of the medical devices involved in the clinical study.

#	Device Name	Manufacturer	Regulatory Status
1	Philips Interventional X-ray System: Azurion 7 M20 FlexArm R2.1	Philips Medical Systems Nederland B.V, Veenpluis 6, 5684 PC, Best, The Netherlands	EU: CE marked US: FDA 510(k) cleared Azurion R2.1: K200917
2	Interventional Workspot R1.6 and future updates as required (workstation containing Interventional Tools software)	Philips Medical Systems Nederland B.V, Veenpluis 6, 5684 PC, Best, The Netherlands	EU: CE marked US: FDA 510(k) cleared K181177
3	AirWaze Investigational Device (version 1.1)	Philips Medical Systems Nederland B.V, Veenpluis 6, 5684 PC, Best, The Netherlands	Investigational device

There is an Investigator Brochure, and Instructions for Use related to AirWaze [REF-1] and [REF-2], respectively.

3.2. Intended Purpose

For a more detailed description of the investigational device including safety precautions and handling, see the Instructions for Use (IFU) [REF-2].

3.2.1. Indications for Use/medical purpose

Device Description

AirWaze Investigational Device 1.1 :

- is a post processing software medical device intended to assist physicians with lung interventions under X-ray guidance;
- enables inspection of 3D reconstructions of the thorax, segmentation of airways and lesions, endobronchial path-planning and overlay of 3D reconstruction with correspondent planning information on live 2D fluoroscopic images;
- provides real-time feedback on device position with respect to the planned path and ablation zone;
- is based on the commercial Interventional Workstation 3DRA products.

Indications for Use

The AirWaze Investigational Device 1.1:

- is intended as an adjunct means to help with the planning and guidance of lung procedures such as biopsy or ablation;
- is intended to be suitable for patients with medical conditions such as where peripheral bronchoscopy is necessary, biopsy is considered a suitable diagnosis procedure, or ablation is considered a suitable therapy;
- is a software medical device and does not interact directly with the patient.

3.2.2. Intended Operator Profile

The AirWaze Investigational Device 1.1 is intended to be used and operated by: adequately trained, qualified, and authorized health care professionals who have understanding of the safety information and emergency procedures as defined by local laws and regulations for radiation workers and staff.
Operators are clinical specialists such as Interventional Pulmonologists, Thoracic Surgeons or Interventional Radiologists who are fully skilled and responsible for sound clinical judgment and for applying the best clinical procedure. The operator may also be an assisting HCP authorized by the physician.

3.2.3. Clinical Environment

The AirWaze Investigational Device 1.1 is a fixed and stationary system that can be used in the control room and in the exam room of an interventional suite or operating room fulfilling the local laws and regulations for radiological X-Ray systems in sterile and non-sterile environments. The system is connected to a Philips Allura or Philips Azurion X-ray system.

3.2.4. General Safety and Effectiveness

To facilitate safe and efficacious operation of the system by a trained healthcare professional, instructions for use are provided as part of the device labelling, as well as training at system handover.

3.2.5. Contraindications

No specific contraindications were identified.

3.2.6. Operating principle

The system uses X-ray image processing for medical imaging. The control mechanisms are input devices and controls as mouse and keyboard in the control room and the TSM at the exam room. The system provides feedback by visual means.

3.2.7. Necessary training and experience needed to use the investigational device

The interventional pulmonologist and the technical team with experience in CBCT-guided navigation bronchoscopy will receive the necessary training to use the AirWaze investigational device. To facilitate safe and efficacious operation of the system by a trained healthcare professional(s), instructions for use are provided as part of the device labelling, as well as training at system handover.

3.3. Materials that will be in contact with tissues or body fluids

Not applicable.

3.4. Device Traceability

Traceability of the investigational device will be achieved during and after the clinical investigation by the following identification:

Table 2. Identification.

Investigational Device	Identifier
AirWaze Investigational Device (version 1.1)	Will be identified by the AirWaze software archive identifier in combination with the related unique software revision number

Records shall be kept to document when the investigational device is received, installed, returned, or uninstalled at the hospital.

4. Justification for the design of the study

4.1. State-of-the-art

Lung cancer remains the leading cause of cancer-related deaths, counting 1.8 million cases worldwide in 2020 and expects to rise in the upcoming years [1,2]. Lung cancer has a high mortality, because of its often already metastatic disease at time of symptom presentation and diagnosis. Computed Tomography (CT) and Positron Emission Tomography (PET) are important imaging modalities in lung cancer diagnosis and show suspected pulmonary lesions as high-density or high-avidity, respectively. These imaging methods are useful, but pulmonary lesions with an intermediate to high risk of malignancy should preferably be diagnosed by image-guided biopsy, such as surgical biopsy or CT-guided transthoracic needle aspiration (CT-TTNA). The latter is a minimally invasive approach that performs a percutaneous biopsy by advancing a needle under CT guidance.

Although CT-TTNA has a high sensitivity for malignancy (approximately 90%), complications such as pneumothorax (pooled complication rate 18.8-25.3%) and associated chest tube placement (6-7%) are relatively high because traversing the thoracic wall and pleura with a needle [3].

Another technology with a well-accepted safety profile is navigation bronchoscopy (NB). This approach is a less invasive and less pneumothorax-inducing technique (pooled complication rate 1.5%, requiring chest tube placement in only 0.6%) using the airways for navigation[4]. Several technological innovations have been developed for endobronchial navigation to pulmonary lesions. Bronchoscopy combined with electromagnetic navigation bronchoscopy (**ENB**), virtual bronchoscopy navigation or robotic assisted bronchoscopy (**RAB**) all achieve good results for navigation, but a second imaging modality is needed for positioning of the catheter and tool-in-lesion confirmation [5–7]. For instance, radial endobronchial ultrasound (rEBUS), fluoroscopy and/or cone-beam CT (**CBCT**) can provide catheter positioning confirmation.

- **ENB** is a minimally invasive, image-guided approach to access lung lesions for biopsy. The NAVIGATE trial evaluated ENB safety and diagnostic yield in a multi-centre cohort study. A recent update of the NAVIGATE trial reported a diagnostic yield of 67.8% overall and 62% for nodules smaller than 20 mm. The reported overall complication rate for pneumothorax is 4.7%, and 3.2% require intervention or hospitalisation[8]. In conclusion, ENB procedures have been proven to have low complication rates, however, the diagnostic yield cannot compete with the diagnostic yield of CT-TTNA.

- **RAB** is a technology that has gained much attention since the introduction of the first system in the US in 2018. Nowadays, there are two systems available in the US market: Auris Monarch and Intuitive Ion. The diagnostic yield of these systems varies between 69.1 and 81.7%, respectively, and have demonstrated low complication rates for pneumothoraxes [5,9].

- The diagnostic yield increases even more, when **CBCT and augmented fluoroscopy** (AF) are involved in navigation bronchoscopy. Pritchett *et al.* Used ENB in combination with CBCT and AF to guide to the lesions. This resulted in a navigation success of over 83% for both small and large lesions [10]. Verhoeven *et al.* Reported a diagnostic yield of 90.6% after experiencing the effect of a learning curve [11]. As additional guidance and confirmation method, r-EBUS was used. In conclusion, utilizing intraprocedural CBCT image guidance—a relatively new technique in interventional pulmonology field—may retain complication risk while further increasing the accuracy (83.7 – 90.6%) of this technology-enhanced navigation bronchoscopy procedure. Aside from its unique ability to acquire intraprocedural three-dimensional (3D) information, deemed valuable for meticulous positioning of tools, the CBCT system can also augment a navigation pathway and lesion position as an overlay on two-dimensional (2D) fluoroscopic imaging. With this unique combination of features, CBCT has the potential to meticulously help guide the endoscopist during the different aspects of the procedure. CBCT-guided NB can provide 3D positioning confirmation and has a diagnostic accuracy of 90% for peripheral pulmonary nodules.

Unfortunately, CBCT-guided NB has a significant learning curve, mainly because of the high cognitive load for the bronchoscopist [11]. Cognitive load is the overall effort expended by individuals in response to a task and is closely related to the usability of devices for medical procedures. A high cognitive load is associated with poor surgical outcomes and represents a bottleneck for learning that directly affects performance and acquisition of competency[12]. In CBCT navigations, the bronchoscopist must mentally reconstruct the patient-specific anatomy including the airways, relevant vasculature, and the lesion, which requires a high cognitive load. This 3D visualization of the bronchial tree and the translation into the rotational catheter progression using AF overlays in different directions increases the cognitive load more and more. This cognitive load diminishes the widespread implementation of this technique. Therefore, there is a need for imaging assistance with easy and advanced software tools for CBCT-guided navigation bronchoscopy.

4.2. Evaluation of (pre)clinical testing

The 3D segmentation of the endobronchial tree based on pre-procedural CT, lesion segmentation, and pathway generation with the AirWaze investigational device (version 1.0) have been evaluated in a preclinical setting. Here, the first-pass navigation success was between 73 and 79% and was 100% in a second pass and overall. Fluoroscopy times were in clinically relevant timeframes. Navigation error, which is defined as the distance from the catheter tip to the bifurcation measured on the confirmatory CBCT, was another important endpoint. These errors were 2.2 ± 1.2 mm *ex vivo* and 4.9 ± 3.2 mm *in vivo* and are more accurate than results reported with ENB. In conclusion, endobronchial navigation was assessed as feasible and accurate with CBCT and AF guidance in both ex vivo and in vivo models [13].

In a clinical feasibility study, the AirWaze investigational device (version 1.0) was used to plan and guide the navigation procedure with CBCT and augmented fluoroscopy of the target lesion, pathway and bronchial tree (Figure 2) [14]. A total of 52 subjects and 59 lesions with an average median lesion size of 19.0 mm (range 7-48 mm) were included in this study. The navigation success was 98.3% and the overall diagnostic yield was 91.4% (91.2% for lesions <20 mm). No severe adverse events related to CBCT NB with the AirWaze investigational device (version 1.0), such as pneumothorax, respiratory failure, were observed. These results are comparable with findings from the same clinical center using a combination of ENB and CBCT with AF of the target lesion for navigation bronchoscopy. These results demonstrate the safety of CBCT and AF guided biopsies of peripheral pulmonary lesions with the AirWaze investigational device (version 1.0) to obtain high diagnostic yields.

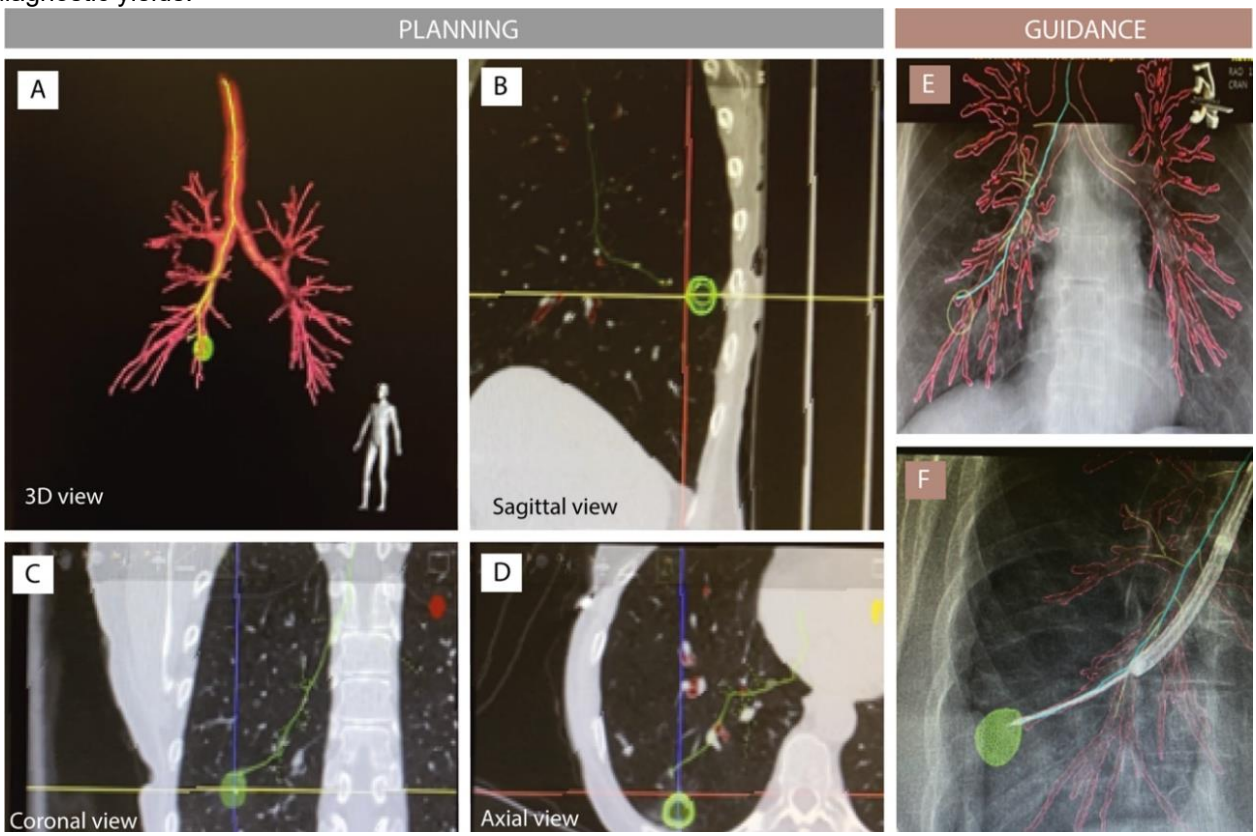

Figure 2. CBCT guidance in bronchoscopy with advanced software tools for peri-procedural planning and 3D image-guidance (AirWaze investigational device, version 1.0). After 3D segmentation of the target lesion and the bronchial tree on pre-operative CT data, the virtual pathway to the target nodule was generated (A-D). Automatic elastic registration of the pre-operative CT with intraprocedural CBCT data enabled live guidance with augmented fluoroscopy views of the airways and virtual pathway to the segmented target lesion I. Confirmation of tool-in-lesion (F).

4.3. Evaluation of clinical data

The AirWaze software tools enable the physician to plan, guide and confirm during navigation bronchoscopy of peripheral pulmonary nodules.

Background clinical application

This study is for subjects with peripheral pulmonary lesions suspicious of malignancy. Traditionally, there are three pathways for lung lesion diagnosis: (*i*) watchful waiting with CT follow-up, (*ii*) minimally invasive diagnostic techniques, and (*iii*) surgical excision with diagnostic analysis. There are two ways to obtain minimally invasive tissue diagnosis, namely via CT-guided TTNA and navigation bronchoscopy (Section 4.1). CBCT-guided navigation bronchoscopy combines navigation guidance with 3D-image confirmation of tool-in-lesion positioning. It can help guide and verify sampling in 3D in near real-time. CBCT-guided NB has proven to have a lower complication rate compared to CT-TTNA while maintaining diagnostic accuracy. However, disadvantages of CBCT-guided NB are the high cognitive load during planning and procedure, and the inherent use of radiation.

The AirWaze Investigational Device (version 1.1) with an improved user interface compared to version 1.0 has been designed to reduce the cognitive load before- and during CBCT-guided NB, and therewith improve overall navigation bronchoscopy procedure accuracy. Furthermore, dedicated low dose imaging protocols have been designed to reduce the radiation dose of intraprocedural 3D imaging (*i.e.* CBCT-FluoroSweep). The improved ease-of-use, reduced cognitive load and tailored radiation protocols for CBCT-guided interventions are anticipated to increase the overall accuracy of the procedure and help implement it in routine clinical practice across institutes fuel the adoption of CBCT-guided NB.

5. Risks and benefits of the investigational device and feasibility clinical investigation

The risk assessment process that Philips follows is in accordance with ISO14971. This will ensure that the level of risk is acceptable prior to the start of the clinical feasibility study.

Benefits
Benefits related to the investigational device compared to state-of-the-art devices are an improved ease-of-use and a reduced cognitive load for the physicians during CBCT-guided navigation bronchoscopy, while maintaining patient safety and a high diagnostic accuracy for peripheral pulmonary nodules.

Future patient benefit (= after clinical feasibility study of CBCT-FS): 3D confirmation of tool-in-lesion with CBCT-FS may result in less radiation dose compared to conventional CBCT and augmented fluoroscopy

There is a possibility that the patient may not benefit from participating in the study.

Risks
Risks related to the AirWaze investigational device 1.1 compared to state-of-the-art devices, the standard of care/procedure, is:

- As the novel AirWaze software will be evaluated by combining a CBCT with immediate FluoroSweep afterwards (with the intention that they will both give similar image information), radiation dose will be increased for staff and patient. The additional fluoroscopy level dose will have a minimal impact on the overall procedure and staff dose.
- Based on incorrect anatomical overlay information, the operator might deploy the catheter/biopsy tool inaccurately. Possible harm is:
  - Bronchial hemorrhage (E0707)
  - Pneumothorax (E0734)
  - Procedure related complications (E21)
  - Delay to treatment/therapy (F05)

The risks of participating in the clinical feasibility study with the AirWaze investigational device are illustrated in Table 3. All risks have been reduced as far as possible and individual residual risks after mitigation are all classified as acceptable, marked by the green zone in *Table 3*. No additional risks were identified when verifying the risk mitigation.

Anticipated adverse device effects are listed in section 15.3 Anticipated adverse device effects (including the steps that are taken to control or mitigate the risks).

Table 3. Overview of the residual risk profile of the investigational device.

Count of Residual Severity		Delta Residual Severity*				
Residual Probability of Harm (PoH) occurrence**		S0	S1	S2	S3	S4
PoH 5	≥ 10 000	0	0	0	0	0
PoH 4	1 000 - <10 000	0	0	0	0	0
PoH 3	100 - <1 000	0	0	0	0	0
PoH 2	10 - <100	2	1	6	0	0
PoH 1	<10	0	0	0	0	0
Grand Total		**2**	**1**	**6**	**0**	**0**

**Severity is defined according to:*
S0 – Negligible: Results in Inconvenience or temporary discomfort not requiring professional medical intervention OR in customer dissatisfaction where there is no injury.
S1 – Minor: Results in injury or temporary impairment not requiring professional medical intervention
S2 – Major: Results in injury or temporary impairment requiring professional medical intervention

S3 – Critical: Results in permanent impairment OR in an injury, which is life-threatening if professional medical intervention is not obtained
S4 – Catastrophic: Directly results in death

*** Probability is defined as likelihood per 1000000 examinations*
PoH–5 – Occurs 'every time' (≥10 000 per 1000000).
PoH–4 – Good chance to occur; considerable certainty to occur (1 000— <10 000 per 1000000).
PoH–3 – Expected to occur from time to time; rarely occurring (100—<1 000 per 1000000).
PoH–2 – Not expected to occur (10— <100 per 1000000).
PoH 1 – Improbable (<10 per 1000000).

There are no possible interactions with concomitant medical treatments.

5.1. Benefit-to Risk rationale

The outcome of the risk management process for the clinical study including the use of the investigational device is that the medical benefits of the device outweigh the risks associated with its use.

There is no unacceptable risk when participating in the clinical study with the AirWaze investigational device. The residual risks for the investigational device use are low and therefore outweighed by the medical benefits as outlined above. The investigational device can be safely used in clinical practice.

6. Objectives

6.1. Primary objective

The primary objectives of this feasibility clinical investigation are to assess the overall system usability of the Philips AirWaze investigational device as measured by the System Usability Score (SUS) and the accuracy of the tool-in-lesion confirmation scan CBCT-FluoroSweep compared to the conventional CBCT.

6.2. Secondary objective(s)

The secondary objectives of this clinical feasibility investigation are:

- To assess intuitiveness of the individual AirWaze features by the physicians.
- To assess performance the following developed algorithms:
  (a) Segmentation bronchial tree on pre-procedural CT.
  (b) Elastic registration of the intraoperative CBCT scans with preprocedural CT scan.
  (c) Automatic device detection on intraoperative CBCT scans.
- To assess the quality of the interventional plan (pre-procedural planning).
- To assess the confidence levels of interventional pulmonologists while using AirWaze (pre-procedural planning).
- To assess the intraprocedural cognitive load of CBCT-guided NB.
- To determine the radiation exposure for patients and staff.
- Report all adverse events, adverse device effects and device deficiencies.

7. Study Design

7.1. General

The AirWaze software tools for CBCT-guided diagnosis of peripheral pulmonary nodules will be studied at the Radboud University Medical Centre with the Principal Investigator described below:

Name Principal Investigator(s)	Name and address investigation site(s)
Erik H.F.M. van der Heijden, MD, PhD Professor of Interventional Pulmonology	Radboud University Medical Center Nijmegen Department of Pulmonary Diseases 6500 HB Nijmegen, The Netherlands

An interview guide will be used to collect data regarding the primary endpoint. Data about the primary endpoints will be collected with semi-structured interviews as described in Appendix I: System Usability Scale (SUS) and Appendix II: CBCT-FS compared to CBCT.

A total of 37 prospectively included subjects in the Intention-To-Treat population are necessary to collect sufficient data for the evaluation of the objectives of this clinical investigation. After applying a drop-out rate of 10% of subjects will be lost, a total of 33 subjects in the Per Protocol population is required. More information on the statistical considerations can be found in Section 8.

7.1.1. Endpoints

The primary and secondary endpoints are based on the objectives (Section 6) and are described below.

Primary endpoints

The system usability will be assessed by using the System Usability Scale (SUS) [15]. An average SUS of greater than 70 will indicate a good usability design of the AirWaze Software solution. The SUS will be measured per operator every 4 procedures.

Image-based tool-in-lesion confirmation accuracy of CBCT-FS is defined as the number of procedures where CBCT-FS scans were adequate to define tool-in-lesion compared to conventional CBCT scans (gold-standard). The image-based tool-in-lesion accuracy is defined as the sum of the number of tool-in-lesion in both the CBCT-FS and CBCT images (i.e. true positives), and the number of no tool-in-lesion confirmation in both the CBCT-FS and CBCT images (i.e. true negatives), divided by the total number of CBCT-FS and CBCT pairs. Image based tool-in-lesion confirmation accuracy of 90% will indicate that the CBCT-FS is postulated to be sufficient for navigation bronchoscopy.

Secondary endpoints

The secondary endpoints of this feasibility clinical investigation are:

- Semi-structured questionnaires to assess intuitiveness of AirWaze features for CBCT-guided biopsy of peripheral pulmonary nodules (Appendix III).
- Quantitative and qualitative assessment of the developed algorithms is assessed through a questionnaire (Appendix IV).
  (a) Segmentation bronchial tree on pre-procedural CT.
  (b) Elastic registration of the intraoperative CBCT scans with preprocedural CT scan.
  (c) Automatic device detection on intraoperative CBCT scans.
- The quality of the interventional planning is defined by comparing the pre-procedural planned navigation trajectory compared to the actual navigation trajectory towards the first lesion (Appendix V).
- Confidence levels of pulmonologists are defined as a score (0-10) to examine the degree of confidence of specialists regarding: (*i*) the localization of the lesion and planned navigation trajectory; (*ii*) reaching the first pulmonary lesion based on the planning (Appendix V).
- The cognitive load of pulmonologists during the navigation towards the first lesion will be measured with the Surgical Task Load Index (SURG-TLX) which is a validated method for measuring cognitive load. The questionnaire is asked after tool-in-lesion confirmation (either rEBUS, CBCT, or CBCT-FS) [12,16,17] (Appendix V).
- Radiation exposure for patients will be measured in effective dose (mSv) and DAP (Gy·cm^2) per procedure including fluoroscopy, CBCT and CBCT-FS radiation dose. The fluoroscopy time (minutes) will be measured as well (Appendix V).
- Radiation exposure for the staff is measured in an average scattered effective dose (mSv) per procedure at hand and chest (Appendix V).
- Report all adverse events (including but not limited to pneumonia, pneumothorax, bleeding/hemorrhage).
- Report all adverse device effects.
- Report all device deficiencies. Device deficiencies that could have led to an SAE need to be reported in the Clinical Study End Report.

7.1.2. Maintenance and calibration

The equipment relevant for the assessment of the clinical investigation is the Philips Azurion C-arm system. Maintenance and calibration of this equipment will be monitored if this is appropriately performed and documented.

7.1.3. Operators / users

In the pre-procedural evaluation of the AirWaze software device, at least three users (n=3) (e.g. interventional pulmonologist experts) will be performing the pre-procedural planning of the CBCT guided peripheral pulmonary nodules biopsies. In the peri-procedural evaluation of the AirWaze software device, at least three certified bronchoscopists (n=3) (e.g. interventional pulmonologist experts) will be performing CBCT guided biopsies of peripheral pulmonary nodules biopsies.

7.2. Investigational device exposure and comparators

During this study, a single investigational device (the AirWaze software device) will be used in this clinical trial, from the Philips workstation connected to the Philips Azurion. The AirWaze device will be used for procedural planning, image-guided navigation, and tool-in-lesion confirmation for bronchoscopic biopsy.

7.3. Subjects

7.3.1. Inclusion and exclusion criteria

In- and exclusion criteria ensure the inclusion of subjects within the intended patient population of the investigational device.

7.3.1.1. Inclusion criteria

In order to be eligible to participate in this study, a subject must meet the following criteria:

- Age 18 years or older at the time of informed consent.
- ASA physical status between 1 and 3.
- Subject is willing and able to give written informed consent for clinical investigation participation prior to the procedure.
- Subject has a pulmonary lesion (*e.g.* a focal rounded opacity mostly surrounded by aerated lung or a ground glass opacity or part- or (sub)solid lesion) with an indication for diagnostic evaluation following current clinical guidelines and/or as decided by multi-disciplinary team consultation.
- Suitable for CBCT-guided endobronchial nodule biopsy under general anaesthesia.
- Pre-procedural (PET-)CT scan is immediately available prior to procedure.

7.3.1.2. Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Aged 17 or younger at the time of informed consent.
- ASA physical status is equal to and greater than 4.
- Not willing or not able to give informed consent.
- Does not indicate diagnostic evaluation with navigation bronchoscopy.
- Not suitable for CBCT-guided endobronchial nodule biopsy via navigation bronchoscopy under general anaesthesia.
- There is no recent pre-procedural (PET-)CT scan available.
- Known bleeding disorders.
- Contra-indication for temporary interruption of the use of anticoagulant therapy (acenocoumarol, warfarin, therapeutic dose of low molecular weight heparins, clopidogrel or analogues, NOACs).
- Known allergy for lidocaine or other allergies interfering with the procedure.
- Uncontrolled pulmonary hypertension.
- Recent and/or uncontrolled cardiac disease.
- Compromised upper airway (*e.g.* concomitant head and neck cancer or central airway stenosis for any reason such that endobronchial access is considered unsafe).
- Potentially confounding drug or device trial clinical study. Co-enrollment in concurrent trials may be allowed if pre-approval is obtained from Philips Clinical Study Manager.
- All vulnerable subjects, such as immune-compromised subjects, subjects lacking the capacity to provide consent, patients in emergencies, pregnant or breastfeeding women, or any other subject who meets exclusion criteria, according to applicable national laws, if any.
- Woman of childbearing potential who is known to be pregnant on admission.
- Any condition that in the judgment of the investigator could impose hazards to the patient if study therapy is initiated or affect the participation of the subject in the study.
- Subject is Philips employee or their family members residing with this Philips employee.

7.3.2. Enrollment and duration

The total duration of the study is expected to take approximately 18 months, from the first patient to the last patient (excluding reporting). The first patient was enrolled in October 2023.

- Subjects are enrolled in the feasibility clinical investigation after they have signed the informed consent form. No study procedures will be performed before this moment.

- Subjects are enrolled in the clinical investigation for the duration of the interventional procedure until 1 week post-procedure. A safety follow-up visit (either by phone or clinic visit) will take place at 1 week (-2 days/+7 days) post procedure.

The clinical investigation is completed when the last subject has undergone CBCT-guided NB and follow-up visit, whether the clinical investigation concluded according to the pre-specified clinical investigation plan or was terminated prematurely.

7.3.3. Number of subjects

A total of 37 prospectively included subjects in the Intention-To-Treat population are necessary to collect sufficient data for the evaluation of the primary and secondary objectives of this clinical investigation. After applying a drop-out rate of 10% of subjects will be lost, a total of 33 subjects in the Per Protocol population is required. More information on the statistical considerations can be found in Section 8.

7.3.4. Procedure for the replacement of subjects

Subjects in the study will be replaced in case of withdrawal of consent or the subject is found illegible for the study after signing the informed consent and before the procedure. The data of these subjects will not be analyzed (per protocol analysis, see section “statistical considerations”).

7.3.5. Subject withdrawal

Subjects can withdraw informed consent at any time for any reason during the clinical investigation. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Normal clinical standard of care will be followed to obtain a diagnosis.

7.4. Procedures

The flowchart for current clinical practice and study practice CBCT-guided navigation bronchoscopy are depicted in *Figure 3* below.

Current clinical practice

- *Pre-procedural*

In current clinical practice, the lesion identification and trajectory planning are performed by interventional pulmonologists who need to mentally reconstruct the navigation trajectory (mind-map) based on the available CT-images in routine DICOM viewers.

- *Intra-procedural*

The procedure starts with an inspection bronchoscopy to examine the trachea and proximal airways. If the tumour is not visible endobronchially, navigation bronchoscopy is continued by advancing a pre-formed curvature catheter through the bronchoscope under image guidance. Advanced imaging with CBCT and AF will expedite catheter guidance through the airways. The CBCT gives feedback about the position of the catheter in a three-dimensional space. Once tool-in-lesion is confirmed with either rEBUS, rapid on-site evaluation (ROSE) and/or CBCT, tissue sampling is performed. If indicated, an EBUS is performed for staging lung cancer.

Study practice

- *Pre-procedural*

In this study, pre-procedural planning will be performed with Philips’ AirWaze software. The CT-scan is loaded into the software system and the airways will be segmented and visualized. The target lesion is segmented with a one-click segmentation by the physician and is followed by a selection of the pathway to the target lesion.

- *Intra-procedural*

As performed routinely, an inspection bronchoscopy is performed at the start of the procedure. The selected pathway to the target lesion from the planning will be registered to and overlayed on the first performed CBCT. This overlay is visible at any time and will help the physician guide to the target lesion. If CBCT is indicated in conventional procedures, a low-dose CBCT-FluoroSweep scan will be performed of the same catheter and tool position. The CBCT-FluoroSweep has the same function as the regular CBCT, but it will be evaluated whether the low-dose CBCT-FluoroSweep is as accurate as the CBCT. Once tool-in-lesion is confirmed with either rEBUS, ROSE and/or CBCT-FluoroSweep (with regular CBCT as gold standard), tissue sampling is performed. If indicated, an EBUS is performed for staging lung cancer.

Follow-up

Safety follow-up visit will take place 1 week post-procedure (+7 days / -2 days). This visit may occur via phone or clinic visit. All adverse events that have occurred until this visit will be collected and monitored, including any prolonged hospital stay because of procedural complications, as well as unexpected complications.

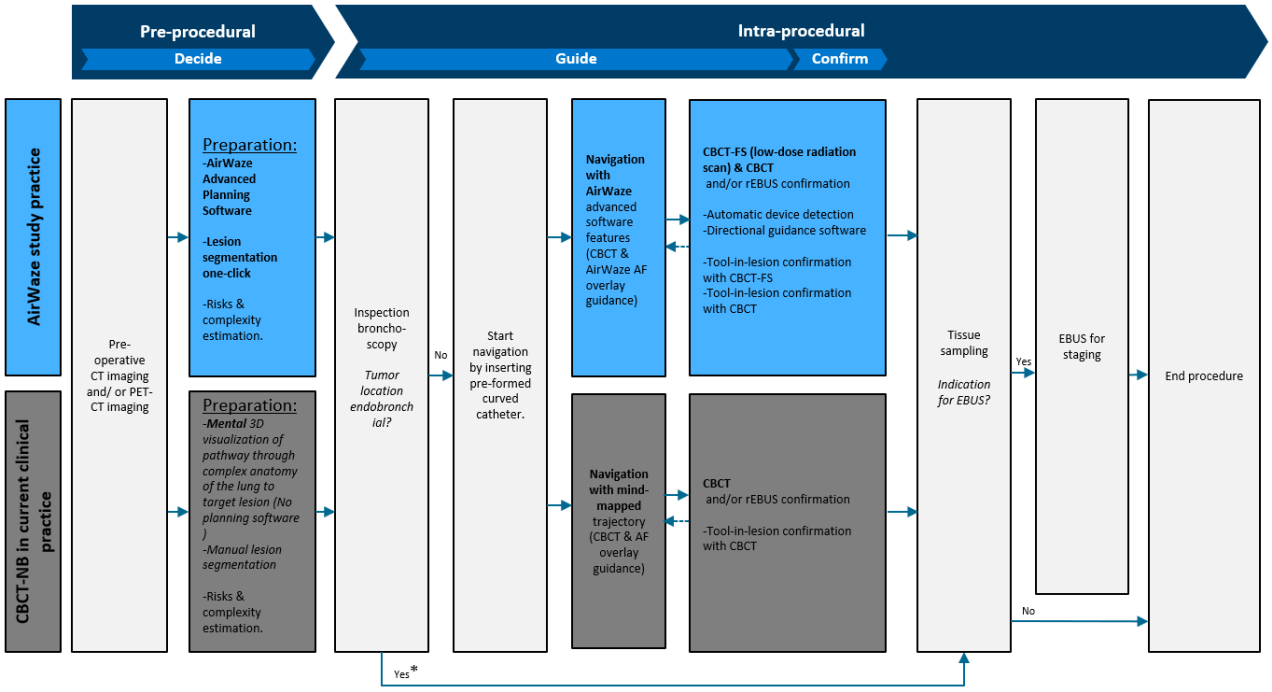

Figure 3. Flowchart of the CBCT-guided navigation bronchoscopy procedure of the current clinical practice (bottom flow) and study practice with the AirWaze investigational device (top flow).
**Will be excluded from the PP population, see section 8.1.*

7.5. Monitoring Plan

Monitoring will be performed by a trained person appointed by Philips to ensure compliance with the feasibility clinical investigation protocol, applicable national regulations and international standards, patient safety and data validity. The Sponsor may designate one or more individuals to monitor the progress of a clinical study. The Sponsor may also delegate the monitoring responsibilities to a third party. However, the Sponsor remains ultimately responsible for the conduct of the study. The Institution is responsible for the appropriate de-identification of subject data. The investigational site should provide access to the source data of the subjects.

The first visit will occur as soon as possible after the first subject is enrolled at each study site. The monitoring schedule is based on the following considerations: enrollment rate, study compliance at the center, the magnitude of data corrections required, the complexity of the feasibility clinical investigation, IRB/MEC request, and audit/inspection.

The monitor activities include:

- Check that the study is conducted, recorded and reported in compliance with the clinical protocol, good clinical practice, and applicable regulations. Acts to oversee the progress of the study.
- Check signed and dated informed consent of the subjects and check that this is signed before any study-related procedures are undertaken.
- Ensure that essential documents (*e.g.,* legal contract, MEC/IRB approval) are maintained in the Site Regulatory File.
- Ensure recording of deviations from protocol and store in Site Regulatory File or e-CRF.
- Ensure that all adverse events and device deficiencies are reported to the sponsor, and all serious adverse events and device deficiencies that could have led to a serious adverse device effect are reported to the sponsor without unjustified delay.
- Ensure that applicable adverse event and device deficiency are reported to the MEC/IRB and Competent Authority (if applicable) within the required timeframe.
- Ensure that the principal investigator is informed and knowledgeable of all relevant document updates concerning the feasibility clinical investigation (e.g., feasibility clinical investigation protocol and Investigator Brochure). Ensure that substantial amendments to the protocol and/or Investigators Brochure are submitted to the MEC/IRB and/or Competent Authority (if applicable) if required by the national regulations.
- Ensure device accountability.

Critical data and processes will be monitored for this study prior to clinical report completion based on a selective monitoring approach. The monitor activity solely involves the review of critical clinical data that effect study endpoints. Data collection for reasons other than to support the protocol-defined endpoints will not be monitored. A site close-out visit will be conducted once the site has completed collecting data for the study.

Details of the monitoring approach and names of the involved monitor(s) will be laid down in the Monitoring Plan.

8. Statistical considerations

8.1. Analysis Populations

The following analysis populations will be defined in this study:

Enrolled Population
The enrolled population is defined as all subjects who signed informed consent during the study.

Intention-to-treat Population
The intention-to-treat population (ITT) is defined as all subjects in the Enrolled Population that have undergone the CBCT-guided navigation bronchoscopy procedure as depicted in *Figure 3* because suspected pulmonary lesions with intermediate to high risk of malignancy in early-stage disease were found on pre-procedural CT scans.

Per Protocol population
The Per Protocol population (PP) is defined as all ITT subjects without major protocol deviations. Protocol deviations will be divided into major protocol and minor protocol deviations. A major protocol deviation is one that may impact subject safety, affect the integrity of study data and/or affect subject's willingness to remain in the study. An example of a major violation is enrolling a participant who did not meet all the inclusion/exclusion criteria or failing to obtain or document informed consent prior to initiation of study procedures. Major protocol deviations would exclude the subject from the PP population.
Minor protocol deviations are those that are not considered to significantly affect the primary endpoint analysis and hence do not warrant subjects' exclusion from the PP population.
Subjects with a tumor location endobronchial found during the inspection bronchoscopy and therefore not require the CBCT-guided navigation bronchoscopy (as displayed in *Figure 3*), will be excluded from the PP population.
The PP population will be the primary population for the analyses as described in study objectives and endpoints.

8.2. Sample Size Justification

A total of 37 patients will be included in this feasibility study. The physicians are familiar with the AirWaze investigational device in a non-clinical setting. The clinical setting will function as clinical and technical de-risking of the software program and the information from this study will be used to design a robust pivotal claim-driven study. Semi-structured questionnaires will be used to assess the overall system usability and the accuracy of the AirWaze CBCT-FS scan. Furthermore, the number of imaging and algorithm failures and the ability to work around quickly will be evaluated. Taking into account a 10% drop-out rate, it is expected by experts that a Per Protocol population of 33 patients is sufficient to de-risk the AirWaze features.

8.3. General Consideration

All results will be summarized using the following descriptive statistics: n, mean with 95% confidence interval (CI), standard deviation (SD), median, interquartile range (IQR), minimum and maximum. Categorical data will be summarized as the number and percentage of subjects in each category (including the category 'missing' if applicable). Generally, percentages will be calculated for missing categories and all percentages will be based on the total number of subjects in the population (denoted by N on the summary tables and figures) Statistical analysis will be performed using SAS (SAS® Life Science Analytics Framework) and/or R statistical software (https://www.r-project.org/).

All data will be listed for the enrolled population. The data will be sorted by subject number.

For summary statistics, the mean and median will be displayed to one decimal place greater than the original value and the measure of variability (e.g., SD) will be displayed to two decimal places greater than the original value. Minimum and maximum will be reported to the same decimal places as the original value. Percentages will be displayed in 1 decimal place. P-values will be reported to three decimal places; p-values less than 0.001 will be reported as $p<0.001$.

8.4. Subject Disposition

Subject disposition, including the total number of subjects evaluated, will be presented. In addition, a listing will be provided with the reasons why the subject was not evaluated.

8.5. Demographics and Baseline Characteristics

Demographics Subjects
Information on age (years), height (cm), and body mass index (BMI) (kg/m^2) will be reported and summarized as continuous data. Gender (male, female, other), and comorbidities will be reported as categorical data.

Demographics Operators
The experience as a medical specialist (years), and the number of CBCT-guided bronchoscopy procedures performed (n) will be reported and summarized as continuous data.

Baseline Subject Characteristics
Lesion size (mm, long axial axis), and volume (mm^3), will be reported and summarized as continuous data (mean ±SD). Location (lobe; LUL, LLL, RUL, RML, RLL), nodule aspect (solid, sub-solid, ground glass opacity, cystic), PET FDG avidity (no uptake, faint, moderate, intense) will be reported as categorical data. Overall ROSE pathology outcome at index procedure will be divided into benign, malignant, atypical cells (non-diagnostic) and not representative biopsy samples.

8.6. Primary objective

Objective
The primary objectives of this feasibility clinical investigation are to assess the overall system usability of the Philips AirWaze investigational device (version 1.1) as measured by the System Usability Score (SUS) and the accuracy of the tool-in-lesion confirmation scan CBCT-FluoroSweep compared to the conventional CBCT.

Primary Endpoints
The system usability will be assessed by using the System Usability Scale (SUS)[15]. An average SUS of greater than 70 will indicate a good usability design of the AirWaze Software solution. The SUS will be measured per operator every 4 procedures that they have operated the AirWaze software solution.

Image-based tool-in-lesion confirmation accuracy of CBCT-FS is defined as the number of procedures where CBCT-FS scans were adequate to define tool-in-lesion compared to conventional CBCT scans (gold-standard). The accuracy is defined as the sum of the number of tool-in-lesion in both CBCT-FS and CBCT, and the number of no tool-in-lesion confirmation in both CBCT-FS and CBCT, divided by the total number of CBCT-FS and CBCT pairs. Image based tool-in-lesion confirmation accuracy of 90% will indicate that the CBCT-FS is postulated to be sufficient for navigation bronchoscopy.

Analysis
The results will be analyzed by using the average SUS and the SUS score development in time. No statistical test will be performed on the SUS scores due to limited data points. A SUS greater than 70 will indicate a good usability design of the AirWaze software device. More information on the SUS questionnaire can be found in Appendix I: System Usability Scale (SUS).

The results will be analyzed by calculating the overall accuracy of the CBCT-FS for tool-in-lesion confirmation. More information on the CBCT-FS scan questions can be found in Appendix II: CBCT-FS compared to CBCT. An additional analysis will be performed within the tool-in-lesion confirmation group. Tool-in-lesion scans are evaluated and subdivided into center-strike and off-center confirmation scans[18], subsequently the accuracy is calculated.

8.7. Secondary objectives

The secondary objectives are descriptive with no performance requirements and no sample size has been calculated.

8.7.1. Secondary objective: Intuitiveness of AirWaze Features

Objective
To assess intuitiveness of the individual AirWaze features by the physicians.

Endpoint
Semi-structured questionnaire to assess intuitiveness of AirWaze features for CBCT-guided biopsy of peripheral pulmonary nodules.

Analysis
The results will be analysed by using the average intuitiveness scores per feature and the intuitiveness score development in time per feature. The intuitiveness of the AirWaze features is indicated as sufficient when the average score per AirWaze feature equals or is higher than 4 (= agree). No statistical test will be performed due to limited data points. More information on the intuitiveness questionnaire can be found in Appendix III: Semi-structured Questionnaires – Assessment of the intuitiveness of AirWaze features.

8.7.2. Secondary objective: Quantitative and qualitative assessment of developed algorithms

Objective
The objective is to assess the performance of the developed AirWaze algorithms. These algorithms are: (i) the segmentation of the bronchial tree based on the pre-procedural CT; (ii) the elastic registration of the pre-procedural CT scan (including segmentations) to the intraoperative CBCT scan(s), and (iii) the automatic device detection on the intraoperative CBCT scans.

Endpoint
Quantitative and qualitative assessment of developed algorithms endpoints:

- The quality of the segmented bronchial tree is defined on a 5-point Likert scale. The segmentation of the bronchial tree is rated independently from the location of the lesion. The segmentation is rated with a Likert score 1 = only trachea, right/left main bronchus, and bronchus intermedius are segmented, to, Likert score 5 = Bronchioles on a distance < 2 cm from the pleura are segmented.
- The quality of the image registration is defined on a 5-point Likert scale from 1 (bad) to 5 (excellent). The image registration is bad if the registration around the target of interest shows large errors. The image registration is excellent if the images are registered accurately around the target of interest.
- The quality of the automatic device detection is defined on a 5-point Likert scale from 1 (bad) to 5 (excellent). The automatic device detection is poor if the device is barely or wrongly detected. The automatic device detection is excellent if the device is detected completely.
- Algorithm failures are defined as the percentage of algorithm failures and the ability to quickly correct/work around them related to 1) segmentation of bronchial tree on preoperative CT scan, 2) image registration of the preoperative CT scan to the intraoperative CBCT and/or CBCT-FS scans or between CBCT(-FS) scans and 3) automatic catheter detection on both CBCT and CBCT-FS.

Analysis
The objective related to the clinical and technical feasibility of CBCT-FS will be evaluated by calculating:

- Quality of the segmented bronchial tree is considered sufficient when the average Likert score equals or is higher than 4. For this categorical variable, counts and percentages will be calculated as well.
- Quality of the image registration is considered sufficient when the average Likert score equals or is higher than 4. For this categorical variable, counts and percentages will be calculated as well.
- Quality of the automatic device detection is considered sufficient when the average Likert score equals or is higher than 4. For this categorical variable, counts and percentages will be calculated as well.
- Algorithm failures are acceptable when in <5 % of the cases for pulmonary lesions algorithm failures related to CBCT or CBCT-FS occurred.

8.7.3. Secondary objective: Quality of the Interventional plan

Objective
To determine the quality of the interventional plan (pre-procedural planning).

Endpoint
The quality of the pre-procedural plan will be determined by comparing the pre-procedural planned navigation trajectory with the actual navigation trajectory towards the first lesion.

Analysis
The objective will be expressed in the percentage of performed navigation trajectories that match the planned pre-procedural navigation trajectory divided by all performed navigation trajectories. The cases where the planned and performed navigation trajectories do not match, the reason for discrepancy will be presented.

8.7.4. Secondary objective: Confidence level

Objective
To assess the confidence levels of interventional pulmonologists while using AirWaze (pre-procedural planning).

Endpoint
Confidence levels of pulmonologists are defined as a score (0-10) to examine the degree of confidence of specialists regarding:

1) the localization of the lesion and planned navigation trajectory.
2) reaching the first pulmonary lesion based on the planning.

Analysis
The level of confidence is scored between 0 and 10, respectively (not confident to very confident). The analysis includes a calculation of the mean, median and standard deviation assuming a normal distribution. This objective succeeds if the mean confidence level is 6.5 or higher for both confidence level scorings. More information about the confidence level can be found in

Appendix V: AirWaze Procedural Analysis.

8.7.5. Secondary objective: Cognitive load during navigation

Objective
To assess the intraprocedural cognitive load of CBCT-guided NB.

Endpoint
The cognitive load of pulmonologists during the navigation of the first lesion will be measured with the Surgical Task Load Index (SURG-TLX) which is a validated method for measuring cognitive load, asked after tissue sampling of the first lesion [12,16,17].

Analysis
The objective will be expressed in the SURG-TLX, which is a score from 0 to 300 for the complexity of the task in the procedure based on a variety of demands. The analysis includes a calculation of the mean, medians and standard deviation assuming a normal distribution. Also the individual demands will be analyzed with calculated means, medians and standard deviations. More information about the cognitive load can be found in Appendix V: AirWaze Procedural Analysis.

8.7.6. Secondary objective: Radiation exposure for patients and staff

Objective
To assess the radiation exposure for patients and staff.

Endpoint
- Radiation exposure for patients will be measured in effective dose (mSv) and DAP (Gy·cm^2) per procedure including disaggregated fluoroscopy, CBCT and CBCT-FS scan dose. Also, the fluoroscopy time (minutes) will be measured**.**
- Radiation exposure for staff is measured in an average scattered effective dose (mSv) per procedure at hand and chest**.**

Analysis
- The radiation exposure for patients will be expressed in an average effective dose and DAP per procedure. The average effective dose and DAP will be higher compared to conventional procedures, but the increase in radiation dose will be relatively low (Appendix VI: Radiation Dose of CBCT-guided NB). The analysis includes a calculation of the mean, medians and standard deviations for effective dose and DAP per procedure.
- The radiation exposure for staff will be expressed in the average effective dose at hand and chest. The average effective dose and DAP will be higher compared to conventional procedures, but this increase in radiation dose will be relatively low (Appendix VI: Radiation Dose of CBCT-guided NB). The analysis includes a calculation of the mean, medians and standard deviations for effective dose at hand and chest.

8.7.7. Secondary objective: Adverse events

Objective
Report all adverse events, except for the unreportable adverse events (section 15.4).

Endpoint
Adverse events, including information on the seriousness, treatment needed, resolution and relevant judgment concerning the causal relationship with the investigational devices, comparator or procedure will be summarized for safety information.

Analysis
The objective is descriptive with no performance requirements and no sample size has been calculated.
All subjects will be included in this analysis.

All adverse events will be presented in a tabular format.

8.7.8. Secondary objective: Adverse Device Effects

Objective
Report all adverse device effects.

Endpoint
Adverse device effects, including information on the seriousness, treatment needed, resolution and relevant judgment concerning the causal relationship with the investigational devices or procedure will be summarized for safety information.

Analysis
The objective is descriptive with no performance requirements and no sample size has been calculated. All subjects will be included in this analysis.

All adverse device effects will be presented in a tabular format.

8.7.9. Secondary objective: Device Deficiencies

Objective
Report all device deficiencies.

Endpoint
Device deficiencies, including any corrective actions taken during the study, if any, will be summarized for safety information. Device deficiencies that could have led to an SAE will be reported in the Clinical Study End Report.

Analysis
The objective is descriptive with no performance requirements and no sample size has been calculated. All subjects will be included in this analysis.

All device deficiencies will be presented in tabular format.

9. Data management

All data will be recorded in a timely manner in the electronic Case Report Form (e-CRF), which will be provided by the sponsor. Conducting a clinical trial and the related use of e-CRFs should not detract from the routine data recording in the source documents. It should be clearly marked in the source medical records of the subject at the trial site that the subject is participating in a clinical trial. Source data must be available to document the existence of the subject and substantiate integrity of trial data collected. Source data must include the original documents related to the trial (*e.g.* procedure image data) and history of subject.
e-CRF will be used to collect medical history, subjects' demographics, procedure-related information, follow-up data, protocol deviations, adverse events and device deficiencies. The e-CRF will be used for data tracking, data review, data cleaning and issuing and resolving data queries. The e-CRF contains an audit trail for recording data and rectifying errors and reconciliation. Entered data will be verified via automatic edit checks and manual review. This e-CRF is a web-based e-CRF which is password protected and is 21 CFR part 11 compliant. The database will be locked at the start of the final analysis. At the end of the study, the data will be stored as a frozen dataset and will be retained.

The data from the subjects will be key-coded (pseudo anonymized) when entered in the e-CRF. The personal information related to the subjects (like name) is kept separately in the enrollment log at the hospital.
Imaging data (Pre-operative (PET-)CT scans, Intraprocedural CBCT scans and (augmented) fluoroscopy scans) will be collected and exported. . Exported data will be de-identified. Procedure date and time will be recorded within the e-CRF and will be used to link the image data to the corresponding e-CRF data.

The following questionnaire information may be recorded directly in the e-CRF and should be considered as source data:

- System Usability Scale (SUS)
- Semi-structured Questionnaires – Intuitiveness of AirWaze features
- Semi-structured Questionnaire – Qualitative assessment of developed algorithms
- AirWaze procedural analysis.

All data will be collected and stored in a secure location.

9.1. Retention period

The investigator shall maintain the records related to this study during the feasibility clinical investigation and for a period according to national regulations. Philips will maintain the records for a period of device End of Life (EoL) plus 15 years after the clinical investigation with the device in question has ended, or, if the device is subsequently placed on the market after the last device has been placed on the market.

The sponsor and principal investigator shall take measures to prevent accidental or premature destruction of these documents.

10. Amendments to the Feasibility Clinical Investigation Protocol

The Investigator Brochure, Clinical Investigation Protocol, CRFs, informed consent form and other subject information, or other clinical investigation documents such as instructions for use shall be amended as needed throughout the clinical investigation and document controlled.
Documentation of changes shall include a description of the changes, justification of the changes and their potential impact on the performance, effectiveness, safety or other endpoints, and identification of the affected documents.
The amendments to the Clinical Investigation Protocol and the subject's informed consent form shall be notified to, or submitted for approval to the MEC and regulatory authorities, if required. The version number and date of amendments shall be documented. The Principal investigator shall refrain from implementing any modifications to the CIP without agreement from the sponsor, MEC and regulatory authorities, if required. Changes to the Clinical Investigation Protocol will be made by the Sponsor.

For non-significant changes of any document already approved by the MEC or competent authority (e.g. minor logistical or administrative changes, changes of monitor(s), telephone numbers, renewal of insurance) not affecting the rights, safety and well-being of human subjects or not related to the clinical investigation objectives or endpoints, will be provided for notification to the MEC and, where appropriate, regulatory authorities, in case required per local regulations.
Significant changes (such as device modifications, and study procedures) shall be agreed upon with the principal investigator. Significant changes shall be submitted to and approved by the MEC and the Competent Authority (if applicable) before implementation. Exempt from this requirement are measures which have to be taken immediately in order to protect the participants.
If the amendment impacts the integrity of the clinical investigation, the data collected before and after the amendment shall be analyzed statistically to assess the effect of the amendment on endpoint analysis. This analysis shall be included in the clinical investigation report.

11. Deviations from the feasibility clinical investigation protocol

The investigator is not allowed to deviate from the feasibility clinical investigation protocol (CIP) neither to enroll subjects that do not comply with all inclusion and exclusion criteria. Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the MEC. Such deviations shall be documented and reported to the sponsor and the MEC as soon as possible. The principal investigator shall promptly report any deviations from the CIP that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances, if required by the MEC or national regulations.

All deviations from the CIP will be documented with date, subject, reason, actions taken and if the deviation affects the subject's rights, safety and well-being or the scientific integrity of the feasibility clinical investigation. The deviation shall be notified to the sponsor as soon as possible via the site monitor. Deviations shall be discussed with the principal investigator(s) or authorized designer. Deviations will be reviewed by the sponsor and in case of serious or repetitive deviations, a corrective action plan may represent a need to initiate a corrective action plan with the principal investigator. In some cases, termination or suspension of the participation of a particular site or investigator.

12. Device accountability

Access to the investigational device shall be controlled and the investigational device shall be used only in the feasibility clinical investigation and according to the feasibility clinical investigation Protocol.
The sponsor shall keep records to document the physical location of the investigational device from shipment of investigational device to the clinical site until return.

The principal investigator shall keep records documenting the receipt, installation, use and return of the investigational device, including the name(s) of person(s) who received, used, or returned the device and the subject identification and date the device was used.

13. Statements of compliance

This feasibility clinical investigation shall be conducted in accordance with the feasibility clinical investigation protocol, and with the ethical principles that have their origin in the Declaration of Helsinki and all applicable regional and/or national regulations. Furthermore, the feasibility clinical investigation conducted in the European Union shall be conducted in accordance with the International Standards ISO 14155 Clinical investigation of medical devices for human subjects - Good clinical practice and the Medical Device Regulation.

This feasibility clinical investigation shall not be started prior to obtaining a favorable opinion from a Medical Ethics Committee (MEC)/Institutional Review Board (IRB) and Regulatory authority (if required). Any additional requirements imposed by the MEC/IRB and/or regulatory authority/FDA shall be followed.

Philips is the sponsor of this study and financing this study. There will be an agreement between the participating site/investigator and Philips IGT-S. Insurance shall be provided for the subjects participating in this clinical trial according to local law.

14. Informed consent process

Informed consent will be obtained from every subject in writing by the investigator or his authorized designee before any study procedures are started. The subject will be informed about all aspects that are relevant to the subject’s decision to participate in the trial, including the trial procedures and risks and benefits of participation in the feasibility clinical investigation. The investigator shall avoid any coercion or undue improper influence on, or inducement of, the subject to participate and shall not waive or appear to waive the subject's legal rights. Information is provided in native, non-technical language, which is understandable to the subject. Ample time should be provided for the subject to read and understand the informed consent form and to consider participation. The informed consent will include personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process. A copy of the signed and dated informed consent form and any other written information will be provided to the subject.

Investigator shall document the process in the subject source document and maintain the signed informed consent at the site.

Subjects who are unable or unwilling to provide informed consent will not be included in the feasibility clinical investigation.

If new information becomes available that might significantly affect the subject's future health and medical care, it shall be provided to the affected subject(s) in written form. If relevant, all affected subject(s) shall be asked to reconfirm their continuing informed consent in writing.

14.1. Incapacitated subjects

Not applicable.

14.2. Minors

Not applicable.

14.3. Subject unable to give informed consent in case of emergency treatment

Not applicable.

15. Adverse event reporting

15.1. Definitions

Adverse Event
ISO14155: Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated
NOTE 1 This definition includes events related to the investigational medical device or the comparator.
NOTE 2 This definition includes events related to the procedures involved.
NOTE 3 For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

EU-MDR: An Adverse Event (AE) is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

Adverse Device Effect
ISO14155: Adverse event related to the use of an investigational medical device.
NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device
NOTE 2 This definition includes any event resulting from use error or intentional misuse of the investigational medical device.

Serious Adverse Event
ISO14155: Adverse event that led to any of the following:
a) death
b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
1) a life-threatening illness or injury, or
2) permanent impairment of a body structure or a body function including chronic disease, or
3) In-patient or prolongation hospitalization, or
4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure of a body function.
5) a chronic disease
c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment

EU-MDR: Any adverse event that led to any of the following:
(a) death,

(b) serious deterioration in the health of the subject, that resulted in any of the following:
(i) life-threatening illness or injury,
(ii) permanent impairment of a body structure or a body function,
(iii) hospitalization or prolongation of patient hospitalization,
(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
(v) chronic disease,
(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect

Serious Health Threat
Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health of subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons
Note 1: This would include events that are of significant and unexpected nature such that they become alarming as a potentially serious health hazard or the possibility of multiple deaths occurring at short intervals.

Serious Adverse Device Effect (SADE)
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect
ISO14155: Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current risk assessment
NOTE Anticipated serious adverse device effect (ASADE) is an effect that by its nature, incidence, severity or outcome has been identified in the risk assessment.

Device Deficiency
ISO14155: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance
NOTE 1 Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.
NOTE 2 This definition includes device deficiencies related to the investigational medical device or the comparator

EU-MDR: Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

15.2. Reporting

Any person identifying an event or information that could have an impact on subjects', users' or other persons' safety, has an obligation to inform the principal investigator and the sponsor of their concerns. Signals from adverse events or device deficiencies that might indicate a serious health threat can be detected by either the sponsor or principal investigator but are evaluated by the sponsor. Any occurrence of a serious health threat can require a specific reporting process according to regulatory requirements.

The investigator shall report to the Sponsor via the adverse event form or device deficiency form in the e-CRF promptly:

a) any Adverse Event
b) any Device Deficiency
c) any new information concerning these events

Investigator will report to the sponsor any Adverse Event of a type identified in the clinical investigation protocol as being critical to the evaluation of the results of that clinical investigation.

Adverse events associated with users or other persons can be documented separately from adverse events associated with the subject, taking into account the data privacy regulations.

The investigator shall report all serious adverse events and device deficiencies that might have led to a Serious Adverse Event if appropriate action had not been taken, the intervention had not occurred, or if circumstances had been less fortunate are reported to the sponsor without unjustified delay.

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 3 calendar days of first becoming aware of the event
Adverse Event	Complete AE eCRF page	• No later than 10 working days after becoming aware of the information • Reporting required through the end of the study
Device Deficiencies 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 eCRF page with all available new and updated information	• Within 3 calendar days of first becoming aware of the event • Reporting required through the end of the study

The investigator shall supply the Sponsor, upon the Sponsor's request, with any additional information related to the safety reporting of a particular event. The Sponsor and Monitor can request access to this information at any time.

Any adverse event experienced by the subject from the time of signing the informed consent until the 1-week follow-up visit will be recorded on the e-CRF. All AEs that are considered related to the investigational device or procedure will be followed until they have abated, or until a stable situation has been reached.

The e-CRF will include the following information for adverse events: date of the adverse event, description, actions taken (including treatment), resolution, assessment of both the seriousness and the relationship to the investigational device, comparator and procedure. Information collected for device deficiencies is the date of device deficiency, whether this could have led to a Serious Adverse Device Effect (SADE) if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.

Sponsor will ensure review of the investigator's assessment of all adverse events and device deficiencies. Ongoing safety evaluation of the investigational device will be done to determine whether risk analysis needs to be updated.
The Sponsor shall report to the competent authority and/or MEC all reportable events and safety updates as required following the reporting requirements and within the specified timelines as required per local legislation.

Where necessary to ensure timely reporting, the sponsor may submit an initial report that is incomplete followed by a complete report.

15.3. Anticipated adverse device effects

Anticipated adverse device effects are described below in *Table 4*.

Table 4. Anticipated adverse device effects.

Anticipated adverse device effects		**Sev erity**	**Likely incidence (PoH)**	**Risk category**	**Mitigation or treatment**
Hazardous situation	**Possible harm**				
Wrong treatment decisions due to errors or missing information in Investigational Device.	Patient exposed to inadequate / inappropriate treatment or diagnostic exposure during clinical use (F10)	S1	PoH 2 - Not expected to occur (10— <100 per 1000000)	Acceptable	Add a message in the user manual stating that feature is not for clinical decision-making.
Permanent malfunction of the Interventional Tool or Interventional Workstation during an interventional procedure due to software or hardware failure. The result is that the user needs to continue the procedure on X-Ray modality without the Interventional Tool.	No Health Consequences or Impact (F26)	S0	PoH 2 - Not expected to occur (10— <100 per 1000000)	Acceptable	No measures need to be taken
The C-arc has been moved in the longitudinal and/or transversal direction invalidating the current registration.	Patient exposed to incorrectly deployed biopsy/ablation tools during clinical use Possible harm is: - Bronchial hemorrhage (E0707) - Pneumothorax (E0734) - Procedure related complications (E21) - Delay to treatment/therapy (F05)	S2	PoH 2 - Not expected to occur (10— <100 per 1000000)	Acceptable	In the IFU, inform the clinical user that the C-arc should not be moved in the longitudinal and/or transversal direction anymore after planning, and what the possible impact is when it happens.
The planned path is not at the right location due to a badly geometrically calibrated system (deviation after a long use), so the geometry space of 3D image is not matching the geometry space of 2D images (fluoro).	Patient exposed to incorrectly deployed biopsy/ablation tools during clinical use Possible harm is: - Bronchial hemorrhage (E0707) - Pneumothorax (E0734) - Procedure related complications (E21) - Delay to treatment/therapy (F05)	S2	PoH 2 - Not expected to occur (10— <100 per 1000000)	Acceptable	Standard (field) service procedures will detect and correct badly calibrated systems.
During roadmap the: - Table has been moved and/or - C-arc has been moved in the longitudinal or transversal direction Consequently, the alignment of the live 2D X-ray images with the 3D volume may be incorrect. The clinical user neglects the visual	Patient exposed to incorrectly deployed biopsy/ablation tools during clinical use Possible harm is: - Bronchial hemorrhage (E0707) - Pneumothorax (E0734) - Procedure related complications (E21)	S2	PoH 2 - Not expected to occur (10— <100 per 1000000)	Acceptable	For C-arc movement: Whenever the system detects, during 3D roadmapping, that the C-arc has been moved, the clinical user will be informed to check the alignment of the overlay of the 2D X-ray images with the 3D volume. For AD5 table: Table is locked before start of 3D roadmapping. Whenever

mismatch and bases his decisions only on the overlay image.	- Delay to treatment/therapy (F05)				the system detects, during 3D roadmapping, that the table has been unlocked, the clinical user will be informed to check the alignment of the overlay of the 2D X-ray images with the 3D volume. For AD7 and Maquet table: Whenever the system detects, during 3D roadmapping that the table is tilted, pivoted or cradled, the user is informed to check the alignment of the 2D Xray images and the 3D volume. (For other movements table tracking is implemented, so additional mitigation is not necessary). In case the system contains a table that does not support table position tracking, the following mitigation is applicable: The clinical user will be informed that in case he moves the table during roadmap the alignment will be lost.
After the biopsy or ablation device planning and alignment with the X-ray system (i.e. XperCT or 2D X-ray registration), - Table has been moved and/or - C-arc has been moved in the longitudinal or transversal direction Consequently, the device planning may have become invalid.	Based on incorrect anatomical overlay information the operator might deploy the device inaccurately. Possible harm is: • biopsy of incorrect tissue • airway or vessel inadvertent rupture by the guide wire • ablation of other essential tissue	S2	PoH 2 - Not expected to occur (10— <100 per 1000000)	Acceptable	Whenever the system detects that the Table and/or C-arc are not in the same position and orientation (head/side) as where the planning has been performed, the clinical user will be informed to check the alignment of the overlay of the 2D X-ray images with the 3D volume.
Patient movement during guidance phase; fluoro overlay on XperCT image and guiding graphics (planned path) do not match because patient, or patient tissue, has moved. As a result, the user will have to perform re-registration to correct the mismatch before proceeding.	Patient exposed to incorrectly deployed biopsy/ablation tools during clinical use Possible harm is: - Bronchial hemorrhage (E0707) - Pneumothorax (E0734) - Procedure related complications (E21) - Delay to treatment/therapy (F05)	S2	PoH 2 - Not expected to occur (10— <100 per 1000000)	Acceptable	In the IFU, inform the clinical user that overlay might become unreliable if the patient moves during acquisition.
Insufficient image quality	No Health Consequences or Impact (F26)	S0	PoH 2 - Not expected to occur (10— <100 per 1000000)	Acceptable	No measures need to be taken.
Large error in CT to CBCT registration which goes unchecked by physician during verification and subsequent biopsy / ablation in close proximity to fissure or pleura.	Patient exposed to incorrectly deployed biopsy/ablation tools during clinical use Possible harm is: - Bronchial hemorrhage (E0707)	S2	PoH 2 - Not expected to occur (10— <100 per 1000000)	Acceptable	The clinical user is shown registration results and explicitly asked to confirm or correct the registration.

	- Pneumothorax (E0734) - Procedure related complications (E21) - Delay to treatment/therapy (F05)				

**Severity is defined according to:*
S0 – Negligible: Results in Inconvenience or temporary discomfort not requiring professional medical intervention OR in customer dissatisfaction where there is no injury.
S1 – Minor: Results in injury or temporary impairment not requiring professional medical intervention
S2 – Major: Results in injury or temporary impairment requiring professional medical intervention
S3 – Critical: Results in permanent impairment OR in an injury, which is life-threatening if professional medical intervention is not obtained
S4 – Catastrophic: Directly results in death

15.4. Unreportable adverse events

The following adverse events do not need to be reported if occurred in the timeframe indicated below.

Table 5. Unreportable adverse events

Unreportable adverse event	Time frame	Rationale
Haemoptysis	<48h	May occur after bronchoscopy by causing damage to the airway walls or taking biopsies in the lung parenchyma. These inconveniences will disappear within 48 hours.
Fever	<48h	May occur after the procedure. Is no reason for alarm and can be treated with antipyretic medication, such as paracetamol.

16. Vulnerable population

This section is not applicable. No vulnerable population.

17. (Early) termination or suspension of the feasibility clinical investigation

There are no provisions or interim analyses planned that can result in early termination of the trial. The principal investigator, MEC, or regulatory authority may suspend or prematurely terminate participation in the clinical investigation at the investigation sites for which they are responsible.
Any signs of unknown or increased risks for the subjects will be discussed by the sponsor and investigator to assess the impact on the subjects and clinical investigation. If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the MEC or regulatory authorities, the sponsor shall suspend the clinical investigation while the risk is assessed.

The sponsor shall terminate the clinical investigation if an unacceptable risk is confirmed.
If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The principal investigator and sponsor shall keep each other informed of any communication received from either the MEC or the regulatory authority.

Serious or repetitive occurrences of deviations from study protocol or non-compliance with regulations may also be the reason for early termination or suspension of a study site. In such situations, there is no change to the planned standard of care follow-up of patients, and follow-up of adverse events.

The competent authority and the MEC will be informed in case of (early) termination or temporarily halt of the study, if required, according to the timelines established in national regulations.

18. Publication policy

It is the intention of the investigator and sponsor to submit the clinical investigation data for publication. Prior to submission, claims on intellectual property will be assessed by the Sponsor.

Criteria for authorship are based on the following ICMJE guidelines: [19]

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

This study will also be registered on clinicaltrials.gov before first enrollment and the content shall be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation. The results will be submitted for publication within 6 months of primary completion date.

19. Bibliography

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-249. doi:10.3322/caac.21660
2. Wild, C.P., Weiderpass, E., Stewart BW. *World Cancer Report: Cancer Research for Cancer Prevention*. Lyon, France; 2021. http://publications.iarc.fr/586.
3. Heerink WJ, de Bock GH, de Jonge GJ, Groen HJM, Vliegenthart R, Oudkerk M. Complication rates of CT-guided transthoracic lung biopsy: meta-analysis. *Eur Radiol*. 2017;27(1):138-148. doi:10.1007/s00330-016-4357-8
4. 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. doi:10.1378/chest.11-1764
5. Chaddha U, Kovacs SP, Manley C, et al. Robot-assisted bronchoscopy for pulmonary lesion diagnosis: results from the initial multicenter experience. *BMC Pulm Med*. 2019;19(1):243. doi:10.1186/s12890-019-1010-8
6. Folch EE, Pritchett MA, Nead MA, et al. Electromagnetic Navigation Bronchoscopy for Peripheral Pulmonary Lesions: One-Year Results of the Prospective, Multicenter NAVIGATE Study. *J Thorac Oncol*. 2019;14(3):445-458. doi:10.1016/j.jtho.2018.11.013
7. Casal RF, Sarkiss M, Jones AK, et al. Cone beam computed tomography-guided thin/ultrathin bronchoscopy for diagnosis of peripheral lung nodules: a prospective pilot study. *J Thorac Dis*. 2018;10(12):6950-6959. doi:10.21037/jtd.2018.11.21
8. Folch EE, Bowling MR, Pritchett MA, et al. NAVIGATE 24-Month Results: Electromagnetic Navigation Bronchoscopy for Pulmonary Lesions at 37 Centers in Europe and the United States. *J Thorac Oncol*. 2022;17(4):519-531. doi:10.1016/j.jtho.2021.12.008
9. Kalchiem-Dekel O, Connolly JG, Lin I-H, et al. Shape-Sensing Robotic-Assisted Bronchoscopy in the Diagnosis of Pulmonary Parenchymal Lesions. *Chest*. 2022;161(2):572-582. doi:10.1016/j.chest.2021.07.2169
10. Pritchett MA, Schampaert S, De Groot JAH, Schirmer CC, Van Der Bom I. Cone-Beam CT With Augmented Fluoroscopy Combined With Electromagnetic Navigation Bronchoscopy for Biopsy of Pulmonary Nodules. *J Bronchology Interv Pulmonol*. 2018;25(4):274. doi:10.1097/LBR.0000000000000536
11. Verhoeven RLJ, van der Sterren W, Kong W, Langereis S, van der Tol P, van der Heijden EHFM. Cone-beam CT and Augmented Fluoroscopy-guided Navigation Bronchoscopy: Radiation Exposure and Diagnostic Accuracy Learning Curves. *J Bronchology Interv Pulmonol*. 2021;28(4):262-271. doi:10.1097/LBR.0000000000000783
12. Kapp CM, Akulian JA, Yu DH, et al. Cognitive Load in Electromagnetic Navigational and Robotic Bronchoscopy for Pulmonary Nodules. *ATS Sch*. 2020;2(1):97-107. doi:10.34197/ats-scholar.2020-0033OC
13. de Ruiter QMB, Karanian JW, Bakhutashvili I, et al. Endobronchial Navigation Guided by Cone-Beam CT-Based Augmented Fluoroscopy without a Bronchoscope: Feasibility Study in Phantom and Swine. *J Vasc Interv Radiol*. 2020;31(12):2122-2131. doi:10.1016/j.jvir.2020.04.036
14. Pritchett M, Schirmer C, van Alfen M, Schampaert S. NOVEL CBCT-BASED NAVIGATION PROTOTYPE FOR BRONCHOSCOPIC BIOPSY OF PERIPHERAL LUNG NODULES: A FEASIBILITY STUDY. *Chest*. 2019;156(A831). doi:10.1016/j.chest.2019.08.794
15. Brooke J. SUS: a retrospective. *J Usability Stud*. 2013;8:29-40.
16. Wilson MR, Poolton JM, Malhotra. Neha, Ngo K, Bright E, Masters RSW. Development and validation of a surgical workload measure: the surgery task load index (SURG-TLX). *World J Surg*. 2011;35:1961-1969.
17. Kennedy-Metz LR, Wolfe HL, Dias RD, Yule SJ, Zenati MA. Surgery Task Load Index in Cardiac Surgery: Measuring Cognitive Load Among Teams. *Surg Innov*. 2020;27(6):602-607. doi:10.1177/1553350620934931
18. RICKMAN OB, MAHAJAN AK, HOGARTH DK, BHADRA K. "TOOL-IN-LESION" ACCURACY OF GALAXY SYSTEM: ROBOTIC-ASSISTED, ELECTROMAGNETIC NAVIGATION BRONCHOSCOPY WITH INTEGRATED TOOL-IN-LESION-TOMOSYNTHESIS TECHNOLOGY: THE MATCH STUDY. *Chest*. 2022;162(4):A2650-A2651. doi:10.1016/j.chest.2022.08.2165
19. ICMJE | Recommendations | Defining the Role of Authors and Contributors. https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html. Accessed September 4, 2022.
20. Rijksinstituut voor Volksgezondheid en Milieu. Gemiddelde effectieve dosis per type CT-onderzoek.
21. REINDERS L, SOTIROPOULOS G, BARANOWSKI R, FONSECA L, LANGEREIS S, LAU K. ULTRA-LOW DOSE CONE-BEAM CT INCREASES POSITIVE DIAGNOSIS RATE OF PERIPHERAL NODULE BRONCHOSCOPY WHILE IMPROVING RADIATION SAFETY. *Chest*. 2022;161(6):A505. doi:10.1016/j.chest.2022.04.039

Appendix I: System Usability Scale (SUS) of AirWaze

The System Usability Scale (SUS) is a reliable tool for measuring the overall usability of a product or service. This score represents how usable and learnable the product or service is. The SUS questionnaire for the AirWaze investigational device will be conducted after every 4 procedures per operator. In total, the SUS questionnaire will be conducted approximately 9 times. The questionnaire consists of a 10-item questionnaire with five response options for respondents; from Strongly agree to Strongly disagree [15].

Please indicate how much you disagree or agree with the following statements:	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
1. I think that I would like to use the AirWaze Software Device frequently.					
2. I found the AirWaze Software Device unnecessarily complex.					
3. I thought the AirWaze Software Device is easy to use.					
4. I think that I would need the support of a technical person to be able to use the AirWaze Software Device.					
5. I found the various functions in the AirWaze Software Device were well integrated.					
6. I thought there was too much inconsistency in the AirWaze Software Device.					
7. I imagine that most people would learn to use these AirWaze Software Device very quickly.					
8. I found the AirWaze Software Device very awkward to use.					
9. I felt very confident using the AirWaze Software Device system.					
10. I needed to learn a lot of things before I could get going with these AirWaze Software Device.					

Appendix II: CBCT-FS compared to CBCT

CBCT-FluoroSweep

1. What is the purpose of the CBCT-FS scan?
    a. Confirm tool-in-lesion
    b. Determine location of the catheter compared to the lesion
    c. Other, ….
2. If confirm tool-in-lesion purpose, can you confirm tool-in-lesion based on the CBCT-FS scan?
    a. Yes, there is tool-in-lesion confirmation.
    b. No, there is no tool-in-lesion confirmation.
    c. Inconclusive, because ……
3. If confirm tool-in-lesion purpose AND tool-in-lesion confirmation, is the tool-in-lesion center-strike or off-center[18]?
    a. Center-strike
    b. Off-center strike
4. To what extent is the CBCT-FS imaging useful to reposition or continue (for all purposes)?

Scan	**1** **Not useful at all**	**2**	**3**	**4**	**5** **Very useful**
CBCT-FS	○	○	○	○	○

5. Did you notice/experience any artefacts or glitches? If yes, please elaborate.
    ……

CBCT (gold-standard imaging)

6. What is the purpose of the CBCT scan?
    a. Confirm tool-in-lesion
    b. Determine location of the catheter compared to the lesion
    c. Other, ….
7. If confirm tool-in-lesion purpose, can you confirm tool-in-lesion (in all three orthogonal orientations) based on the CBCT scan?
    a. Yes, there is tool-in-lesion confirmation in all three orthogonal orientations.
    b. No, there is no tool-in-lesion confirmation.
    c. Maybe, the quality of the CBCT scan is not sufficient to determine tool-in-lesion confirmation.
8. If confirm tool-in-lesion purpose AND tool-in-lesion confirmation, is the tool-in-lesion center-strike or off-center[18]?
    a. Center-strike
    b. Off-center
    c. Lesion is too small to define center-strike or off-center*
9. Did the CBCT scan change your plan based on the CBCT-FS?
    a. Yes
    b. No
10. Did you notice/experience any artefacts or glitches? If yes, please elaborate.
    ……

* The lesion size is comparable to the catheter size.

Appendix III: Semi-structured Questionnaires – Assessment of the intuitiveness of AirWaze features

The AirWaze study is focused on researching the intuitiveness of the different AirWaze features. These semi-structured questionnaires will be conducted after every 4 procedures per operator.

The AirWaze software feature is **intuitive (from a clinical perspective) to use:**

AirWaze feature	**1 Strongly disagree**	**2 Disagree**	**3 Neutral**	**4 Agree**	**5 Strongly agree**
Advanced planning software	○	○	○	○	○
Augmented fluoroscopy	○	○	○	○	○
Automatic device detection	○	○	○	○	○
Directional guidance software	○	○	○	○	○
CBCT-FluoroSweep		○	○	○	○

Additional questions:

1. Is the information displayed visible/readable? If not, what could be improved?
    a. Yes
    b. No, because ….....
    c. Other, ….....

2. Was the relevant information that you need in the decision-making visible? If yes, what was most important information for you? If not, what could be improved?
    a. Yes, ….....
    b. No, because ….....
    c. Other, ….....

3. Based on your experience, what aspects of the AirWaze software solution are most valuable to you?

    ……

4. What is still missing in the AirWaze software solution and/or what feature should still be further improved?

    ……

5. What are the top three **advantages** that you experienced when using the AirWaze investigational device?
    a. _____
    b. _____
    c. _____
6. What are the first three **disadvantages** that come to your mind when using the AirWaze investigational device?
    a. _____
    b. _____
    c. _____
7. Any other comment?

……

Appendix IV: Semi-structured Questionnaire for quantitative and qualitative assessment of the developed algorithms

The quality of the algorithms will be assessed through this questionnaire and will be conducted after every procedure per operator.

Advanced planning software

The advanced planning software contains two major algorithms for: 1) segmentation of the bronchial tree, and 2) image registration.

1. Segmentation of the bronchial tree

The segmentation of the bronchial tree is rated independently from the location of the lesion.

- **1**: Only the trachea, right/left main bronchus, and bronchus intermedius are segmented.
- **2**: RB1 t/m RB10 and LB1 t/m LB10 are segmented.
- **3**: Few (1-2) branches beyond the RB or LB branches are segmented.
- **4**: More (≥ 3) branches beyond the RB or LB branches are segmented to 2 cm from the pleura.
- **5**: Bronchioles on a distance < 2 cm from the pleura are segmented.

a. Please rate the quality of the segmented bronchial tree on the preoperative CT scan:

1	2	3	4	5	Segmentation failed
Please elaborate:					

b. Based on the segmentation of the bronchial tree, is there a bronchus sign?
   a. Yes, there is a bronchus sign.
   b. No, there is no bronchus sign.
   c. Cannot be determined, because insufficient level of bronchial tree segmentation.

c. If not sufficient level of bronchial tree segmentation: Do you have any clue what was the origin of the unacceptable segmentation?

……..

d. Did you notice/experience any glitches? If yes, please elaborate.

……..

2. Image registration

The image registration is bad if the registration around the target of interest shows large errors. The image registration is excellent if the images are registered accurately around the target of interest.

The image registration is evaluated between the different CBCT-scans made during the procedure. The most recent acquired image is the fixed image, and the older acquired image is the moving image.
In future AirWaze implementation, it is desirable to replace the CBCT with the low-dose CBCT-FS. In those procedures one normal-dose CBCT is acquired. The navigation trajectory and lesion segmentations are moved from the CBCT image to the CBCT-FS images. If there are less CBCT(-FS) performed, the image registration is addressed as N/A.

a. Please rate the quality of the image registration at the location of the lesion:

Image registration between moved and fixed scans	**1 Bad**	**2 Poor**	**3 Fair**	**4 Good**	**5 Excellent**	**Image registration failed**
Pre-op CT --> CBCT1	○	○	○	○	○	○
CBCT1 --> CBCT-FS1	○	○	○	○	○	○
…… --> …….....	○	○	○	○	○	○
…… --> …….....	○	○	○	○	○	○
…… --> …….....	○	○	○	○	○	○

b. If not acceptable level of image registration: Can it be corrected manually? And do you have any clue for the origin of the unacceptable levels of image registration?
……..

c. Did you notice/experience any glitches?
……..

Automatic device detection

The automatic device detection is poor if the device is barely or wrongly detected. The automatic device detection is excellent if the device is detected completely.

1. Please rate the quality of the automatic catheter detection during the procedure after acquiring a CBCT scan:

Scan	**1 Bad**	**2 Poor**	**3 Fair**	**4 Good**	**5 Excellent**	**Automatic device detection failed**
CBCT1	○	○	○	○	○	○
CBCT-FS1	○	○	○	○	○	○
……	○	○	○	○	○	○
……	○	○	○	○	○	○
……	○	○	○	○	○	○

2. If not acceptable level of automatic device detection. What is in your view the origin of the unacceptable levels of automatic device detection?

   ……..

3. Did you notice/experience any glitches? If yes, please elaborate.

   ……..

Appendix V: AirWaze Procedural Analysis

PART A: Pre-Procedural Planning

OPERATOR: **STUDY CODE:**

1) Time start planning? *(Measured from opening preoperative CT scan OR from opening AirWaze)*	… : …
2) Catheter curvature for navigating to target lesion?	○ 180 ° ○ Medial ○ Other, please specify...
3) Bronchus sign?	○ Yes ○ No ○ Maybe
4) Pulmonary branch for navigation	○ RB 1 ○ RB 2 ○ RB 3 ○ RB 4 ○ RB 5 ○ RB 6 ○ RB 7 ○ RB 8 ○ RB 9 ○ RB 10 ○ LB 1+2 ○ LB 3 ○ LB 4 ○ LB 5 ○ LB 6 ○ LB 8 ○ LB 9 ○ LB 10 ○ Anatomical deviation: ……..
5) How would you describe your planned trajectory? Be as specific as possible. *(In the post-procedural questionnaire, you will evaluate whether your trajectory prediction was accurate).*	……

6) Time end planning? *(Measured till the closing of the pre-operative CT scan during the pre-procedural planning (e.g. control group) OR till closing AirWaze).*	… : …
7) Total planning time?	…….. minutes of planning time
8) How **complex** was the lesion localization and trajectory planning, to the first target lesion?	Low 0 1 2 3 4 5 6 7 8 9 10 High
9) How **confident** are you that you have accurately localized and planned the trajectory to the first pulmonary target lesion?	Low 0 1 2 3 4 5 6 7 8 9 10 High
10) Based on the planning, how **complex** do you expect the CBCT-guided bronchoscopy towards the first lesion to be?	Low 0 1 2 3 4 5 6 7 8 9 10 High
11) Based on the planning, how **confident** are you that you are going to successfully reach the first pulmonary target lesion?	Low 0 1 2 3 4 5 6 7 8 9 10 High
12) Comments regarding the pre-procedural planning? (*e.g.* quality (PET-)CT, software bugs, distractions)	.....

PART B: Intra-procedural navigation SURG-TLX Form

OPERATOR: **STUDY CODE:**

1) How would you rank the demands related to the **navigation to the first target pulmonary lesion** from less important to most important demand (scale 0 to 5)? You are only allowed to use every number once.

- ○ Mental demand: ……
- ○ Physical demand: ……
- ○ Temporal demand: ……
- ○ Task complexity: ……
- ○ Situational stress: ……
- ○ Distractions: ……

		0					5					10					15					20	
1A) Mental demands: How mentally fatiguing was **the navigation**?	Very Low																						Very High
1B) Physical demands: How physically fatiguing was **the navigation**?	Very Low																						Very High
1C) Temporal demands: How hurried or rushed was the pace of **the navigation**?	Very Low																						Very High
1D) Task complexity: How complex was **the navigation**?	Not Very Complex																						Very Complex
1E) Situational stress: How anxious did you feel while performing **the navigation**?	Not Very Anxious																						Very Anxious
1F) Distractions: How distracting was the operating work environment during **the navigation**?	Not Very																						Very

PART C: End-procedural Form

OPERATOR: **STUDY CODE:**

1) Was the lesion targeted successfully?	○ Yes ○ No
2) Curvature catheter (for target lesion)?	○ Medial ○ 180 ° ○ Other
3) Does the performed navigation trajectory match the trajectory as planned in the pre-procedural form?	○ Yes ○ No
4) Which situation matches the performed navigation trajectory compared to the pre-procedural trajectory of the operator? *The performed trajectory…..*	○ *fully matches the planned trajectory.* ○ *bifurcates different late in the navigation.* ○ *bifurcates different early in the navigation.* ○ *is mispositioned.* ○ *has a transparenchymal route instead of an endobronchial route.* ○ *has an endobronchial route instead of a transparenchymal route.* ○ *does not reach the target at all.* ○ *is hard to compare with the planned trajectory, because of atelectasis or displacement of the lesion.* ○ *Other, ……*
5) To what extent did the planning contribute to reaching the first target lesion?	Low 0 1 2 3 4 5 6 7 8 9 10 High
6) Effective dose fluoroscopy and time fluoroscopy radiation during navigation and confirmation of first target lesion?	…… mSv …… Gy*cm^2 …… fluoroscopy time (s)
7) Effective dose CBCT and No. of CBCT scans during navigation and confirmation of first target lesion?	…… mSv …… Gy*cm^2 …….. CBCT scans (n)
8) Effective dose CBCT-FS and No. of CBCT-FS scans during navigation and confirmation of first target lesion?	….. mSv …… Gy*cm^2 …….. CBCT-FS scans (n)

9) Average (scattered) radiation dose staff (main operator)?	..... mSv (ring dosimeter)	..... mSv (chest dosimeter)
9) ROSE pathology outcome	○ Malignant ○ Atypical cells	○ Benign specific ○ Benign non-specific ○ Not representative
10) Patient Safety issues? *(To be reported in the Clinical Study End Report)*	○ Yes, adverse events, namely: ..... ○ Yes, adverse device effects namely: ..... ○ Yes, device deficiencies, namely:	
12) Comments regarding the AirWaze software tools during the procedure? *(Quality CBCT or CBCT-FS scans, software bugs, distractions in OR, other)*		

Appendix VI: Radiation Dose of CBCT-guided NB

Besides the learning curve related to the high cognitive load of CBCT-guided NB in current clinical practice, the overall radiation exposure is a point of concern in image-guided interventions. Literature studies have reported on radiation exposure with CBCT and AF in interventional pulmonology. For instance, Casal *et al*. reported a dose area product (DAP) and effective dose of 64.6 Gycm^2 and 11-29 mSv per procedure, respectively [7]. More recently, Verhoeven *et al*. reported on procedural radiation exposure during CBCT-guided bronchoscopy for biopsy of peripheral lung nodules [11]. The procedural radiation dose was initially 47.5 Gy·cm^2 (effective dose: 14.3 mSv) and gradually reduced to 25.4 Gy·cm^2 (effective dose: 5.8 mSv), due to increased experience and different fluoroscopic and CBCT protocols including the latest Philips Azurion system. The reduction in fluoroscopic DAP was highest, from 19.0 Gy·cm^2 (effective dose: 5.2 mSv) to 2.2 Gy·cm^2 (0.37 mSv, 88% reduction), despite a significant increase of fluoroscopy time [11]. In comparison, a diagnostic CT scan of the thorax has an average effective dose of 7.8 mSv [20]. Even though the radiation exposure of CBCT-guided NB is acceptable, the ALARA principle (*As Low As Reasonably Achievable)* must be maintained. Radiation exposure is encountered to a learning curve, meaning that with an increased level of performance, the radiation exposure decreases [11,21].

The procedural radiation dose in the study set-up of Verhoeven *et al.* can be divided into the Fluoroscopy DAP and the CBCT DAP[11]. The low dose fluoroscopy DAP using the Azurion system was on average 2.2 Gy·cm^2 in total per procedure with 935 seconds of fluoroscopy time per procedure (n=43). The DAP per CBCT rotational acquisition using the Azurion system was for the original dose protocol 11.6 Gy·cm^2 using on average 2.25 acquisitions per procedure resulting in a total DAP of 28.2 Gy·cm^2 (n=13). Additionally, for the low dose protocol the average DAP was 8.02 Gy·cm^2 using on average 2.93 acquisitions per procedure resulting in a total DAP of 25.4 Gy·cm^2 (n=30). The relevant data from this study are provided in Table 6.

Table 6. Radiation exposure of CBCT-guided NB[11]

Sample size	System	Fluoroscopy			CBCT			Total DAP
		Protocol	DAP	Time (s)	Protocol	DAP/ acquisition	Acquisitions	
n=13	Azurion	Low dose	2.2	935	Normal dose	11.55	2.25	28.2
n=30	Azurion				Low dose	8.02	2.93	25.4

The estimated radiation exposure of the AirWaze study is depicted in Table 7.

- Radiation exposure assumptions:
  - Verhoeven *et al.* has reported the radiation exposure of CBCT-guided navigation bronchoscopy for biopsy of PPNs. An average fluoroscopy time of 935 seconds was used for real-time navigation and sampling guidance. The average total DAP for these 935 seconds was 2.2 Gycm^2.
  - It is expected that the implementation of AirWaze CBCT-FS will reduce the fluoroscopy time and thus the overall DAP. This benefit of an expected reduction in fluoroscopy time is <u>not</u> considered in the calculations as depicted in Table 7.

- AirWaze and CBCT-FS are implemented for testing the clinical and technical feasibility. The first performed scan during a procedure is a conventional CBCT. In case additional scans are required, a CBCT-FS scan is performed on top of the conventional imaging protocol. A comparison between the additional CBCT and CBCT-FS is then made. The DAP per CBCT-FS acquisition is less than 1.45 Gy·cm^2 based on preclinical studies.

Table 7. Expected estimated radiation exposure during this Feasibility Clinical Investigation

	Low Dose Fluoroscopy		CBCT			CBCT-FS*		Total DAP ($Gy \cdot cm^2$)
	DAP ($Gy \cdot cm^2$)	Time (s)	Protocol	DAP ($Gy \cdot cm^2$) / acq.	Acqs.	DAP ($Gy \cdot cm^2$) / acq.	Acquisitions	
CBCT-NB w/o AirWaze	2.2	935	Normal dose	11.55	1	-	-	20.8-37.8
			Low dose	8.02	1-3			
Study (n=22)	2.2	935	Normal dose	11.55	1	-	-	22.3-42.2
			Low dose	8.02	1-3	1.45	1-3	

* The number of CBCT-FS scans are expected to be equal to the number of additional low dose CBCT scans performed (=total number of CBCT minus one).

In current standard of care of CBCT-guided NB, the staff is exposed to scattered radiation during the 935 seconds of fluoroscopy. All staff members are leaving the operation room (OR) during CBCT-image acquisition and are therefore not exposed to scattered radiation. During CBCT-FS, it is not required for the staff to leave the room. This is one of the reasons why the scans can increase the staff dose. The expected increase will not be visible in this study, since the staff will already leave the OR during CBCT, and will most likely be outside the OR during the CBCT-FS at that same moment. Some measures and expected effects will diminish radiation exposure for staff, such as the use of lead shields and increasing distance to the source (inversed quadratic relationship). It is also expected that the total fluoroscopy time will be reduced by using AirWaze and CBCT-FS since navigation guidance and tool-in-lesion visibility has been improved. To measure the staff (scattered) radiation dose, we apply two dosimeters (head and chest) on all attending operators during all procedures performed in this study to measure the exact effects.

The dose area product (DAP) and effective dose will be measured, as proposed by Verhoeven *et al.* [11]. During this study, the indirect radiation bundle for the staff closest to the CBCT is measured at the hand and chest with validated dosimeters which are commercially available.

Appendix VII: Roles, responsibilities and qualifications of Investigators

Roles and Responsibilities of investigators

The investigator:
a) has the responsibility to implement and manage the day-to-day conduct of the clinical study as well as to ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical study.
b) shall ensure proper communication with the EC as described in ISO14155
c) shall ensure compliance with the applicable regulatory requirements and ethical principles for the process of obtaining informed consent as described in ISO14155.
d) shall conduct the clinical investigation in compliance with the clinical protocol as described in ISO14155.
e) shall provide adequate medical care as described in ISO14155.
f) shall ensure safety reporting as described in ISO14155.
g) has the required number of eligible subjects needed within the agreed recruitment period, and
h) can demonstrate that the investigation site has one or more qualified investigators, a qualified investigation site team and adequate facilities for the foreseen duration of the clinical investigation.

Qualification of the investigator

Before the start of the study, the principal investigator shall be qualified in accordance with ISO14155:
a) by education, training and experience to assume responsibility for the proper conduct of the clinical investigation.
b) by experience in the field of application and training in the use of the investigational device under consideration.
c) by the disclosure of potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results, and
d) be knowledgeable about the method of obtaining informed consent.