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Sammenligning af kamera tube (VivaSight) med almindelig dobbeltløbet tube (Shiley) til thorax kirurgiske indgreb.

Et klinisk og økonomisk studie
CIS-009

A Randomized Controlled Study Comparing the VivaSight Double-lumen Tube with a Conventional Double-lumen Tube in Adult Patients Undergoing Thoracic Surgery

A clinical and economic evaluation
CIS-009

To be initiated: Summer/Fall 2018

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Contents

1. INTRODUCTION

Single-lung ventilation refers to the mechanical separation of ventilation between the two lungs, resulting in ventilation of only one lung. This technique is used either to facilitate exposure of the surgical field or to anatomically isolate one lung from a pathologic process of the other lung. The two most common methods of single-lung ventilation for thoracic surgery are utilisation of a Double-Lumen Tube (DLT) or a single-lumen endotracheal tube with a bronchial blocker (1).

Single-lung ventilation is required in several clinical situations and for various surgical procedures. Perhaps the most frequent indication is thoracic surgery during which single-lung ventilation and collapse of the operated lung facilitate the operation. DLTs are the most common approach to single-lung ventilation. The DLT consists of a proximal tracheal end and a distal bronchial end, reaching into either the left or right side of the lung (2).

However, DLTs are difficult to insert and they often move during surgical lung manipulation or when changing the position of the patient which can compromise the patient safety and cause life-threatening complications for the patient (2). In order to avoid that and secure a more proper placement of the tube VivaSight-DL have been introduced. VivaSight-DL has an integrated camera allowing continuous visualization of its position in the trachea. Furthermore, the VivaSight-DL is the world's only fully disposable tube with an integrated imaging system and ventilation for accurate placement and consistent, real-time airway control. Lastly, as VivaSight-DL is a single-use device it prevents contamination of the ventilated lung (3,4).

The CIP was made according to the Council Directive 93/42 EEC of 14 June 1993 and amendment 2007/47/EC (5), the guidelines set out in ISO 14155 (6), ISO 14971 (7) and the Helsinki Declaration (8).

2. AIM OF THE INVESTIGATION

The aim of this study is to make a health economic evaluation comparing novice physicians use of VivaSight-DL and a conventional DLT for single-lung ventilation during thoracic surgery. To do so, clinical outcomes that influence the cost of the procedures, including the incidence of fibreoptic bronchoscope (FOB) use, time and need of tube repositioning (see section 4), will be assessed and analysed.

3. HYPOTHESIS

Is VivaSight-DL more cost-effective than a conventional DLT?

H_0: VivaSight-DL is not more cost-effective than a conventional DLT because the incidence of FOB use is not lower for Vivasight-DL

H_A: VuvaSight-DL is more cost-effective than a conventional DLT because the incidence of FOB use is significantly lower for VivaSight-DL resulting in workflow optimization.

4. END POINTS

Primary end-point:

- Number of times where fiberoptic confirmation of tube position during intubation or surgery is needed

Secondary end-points:

- Intubation time (seconds)
  - Time starts: when introducing the laryngoscope blade into the subject's mouth.
  - Time stops: when correct bronchial cuff placement is confirmed by capnography

- Number of intubation attempts
  - Intubation attempt is defined as the number of intubation attempts until successful intubation is accomplished. If the endotracheal tube is incorrectly placed and the tube is withdrawn from the subjects throat it counts as one attempt.
  - If more than three intubation attempts are used the intubation is defined as a failure and the subject is excluded from the study.
- Number of times incorrect placement of the tube is prevented during intubation
  - Prevention of repositioning is a corrective action that ensures optimal ventilation of the subject without having to move the tube after the bronchial cuff is inflated. An example of a corrective action during intubation could be change of the tube direction if it starts to enter the right main bronchi instead of the left main bronchi when advanced down the throat.
- Number of times the tube needs to be repositioned during intubation
  - In this study, repositioning is defined as the action where the bronchial cuff needs to be deflated to move the tube into the right position.
- Number of times where the physician prevents repositioning of the tube during surgery
  - Prevention of repositioning is a corrective action that ensures optimal ventilation of the subject without having to move the tube after the bronchial cuff is inflated. An example of a corrective action during surgery could be optimization of the cuff sealing by deflating and inflating the cuff without moving the tube.
- Number of times the tube needs to be repositioned during surgery.
  - In this study, repositioning is defined as the action where the bronchial cuff needs to be deflated to move the tube into the right position.
- Repositioning time (seconds) during surgery
  - In this study, repositioning is defined as the action where the bronchial cuff needs to be deflated to move the tube into the right position.
  - Time starts: when the syringe is attached to the valve to deflate the bronchial cuff
  - Time stops: when correct bronchial cuff placement is verified by capnography
- Rate of restriction on the surgical procedure during repositioning of the tube
  - One of the following statements is chosen:
    - Not restricted
      - The surgical procedure is not restricted at all, the surgeon continues to work full speed
    - Restricted
      - The surgical procedure continues but with limited speed, the surgeon's ability to perform the procedures is affected.
    - Completely restricted
      - The surgical procedure is completely restricted (surgical procedure is paused), the surgeon is not able to work at all.
- Number of times the backup anesthesiologist is called into the operating room for assistance
- Time the back-up anesthesiologist spends on the procedure
  - Time starts: when the backup anesthesiologist answers the phone
  - Time stops: when the backup anesthesiologist leaves the operating room

Tertiary end-points:

- Qualitative measures (questions to the subject) (appendix V)
  - Any side effects from the surgery
  - Daily function level prior surgery
- Qualitative measures (questions to the person who intubates) (appendix VI)
  - Ease of tube placement (very easy, easy, acceptable, difficult, very difficult)
  - How would you rate the overall perception of quality and functionality of the tube (VivaSight-DL or conventional DLT)? (Very poor, poor, acceptable, good, very good)
  - Would you prefer to use VivaSight-DL or conventional DLT in the future (VivaSight-DL/conventional DLT)

5. DESIGN OF INVESTIGATION

5.1 Design of investigation

A randomized, controlled single-centre investigation comparing the VivaSight-DL and the conventional DLT at a teaching hospital. A pilot study including up to 10 subjects will be performed prior to the investigation is initiated (see section 7.1). The investigation will include a total of 50 adult subjects (25 subjects in each group) admitted to department V at OUH with established indication of single lung ventilation.

The objective of the investigation is to compare the number of times the tube position needs to be verified with a scope and relevant costs between VivaSight-DL and conventional DLT in a cost-effectiveness analysis. Furthermore, procedure time, intubation attempts and repositioning will be assessed (see section 4. End Points).

The study will start to recruit subjects within four weeks after Ethical Committees approval and nine months ahead or until 50 subjects have been recruited. If the number of subjects cannot be included in time, the sponsor and Principal Investigator will decide if the study should be closed.

Each subject enrolled in the investigation can only participate in the investigation once. The study duration for each subject is counting from the indication of the need of a single lung ventilation procedure until the subject has completed the questionnaire. Only one test device should be used per subjects (VivaSight-DL or conventional DLT).

Only subjects who can be clinically evaluated as eligible for a single lung ventilation procedure i.e. complies with the listed inclusion and exclusion criteria may be included in the investigation. If subjects or their legal representatives do not consent to the investigation or if the subject is not assigned a novice physician to perform the procedure, the procedure will be performed regardless – however off this investigation. A Case Report Form (CRF, appendix III) must be filled in for each subject that is assigned a novice physician to perform the intubation and has signed the Informed Consent (appendix II), and therefore is included in the investigation. After the surgery the subjects will be asked to answer a questionnaire regarding health-related life quality and side effects from the procedure (appendix IV). If the subject cannot give feedback, the reason is stated in the questionnaire.

Physicians with experience in less than 50 DLT placements in patients are included in the investigation. The learning curve is accounted for by giving all physicians a training in performing DLT intubation before participating in the study. During the training, the physicians will perform at least 10 conventional DLT placements and three VivaSight-DL placements in manikin. Investigational product training will be recorded on a separate form and stored in the Sponsor File.

The investigation center is regularly performing single lung ventilations and has a patient flow of minimum 5 per week. The center is willing to allow insight to the departments' general costs in relation to surgeries with single-lung ventilation. The extent of necessary cost data depends on the sites' organisational setup and subsequently the resources spent during single-lung ventilation and reprocessing of bronchoscopes. Data is collected after the entire process related to single-lung ventilation has been thoroughly mapped via monitoring and interviewing key personnel. Cost data related to single-lung ventilation includes but is not excluded to personnel costs, capital costs related to bronchoscopy, reprocessing and performing single-lung ventilation, maintenance costs, cost of service agreements, cleaning verification costs and administrative costs.

5.2 Sample size

The pilot study will include a maximum of 10 adult subjects undergoing a surgery with single-lung ventilation
- Maximum 5 subjects using VivaSight-DL
- Maximum 5 subjects using conventional DLT

The study will include 50 adult subjects undergoing a surgery with single-lung ventilation.
- 25 subjects using VivaSight-DL
- 25 subjects using conventional DLT

5.3 Expected time schedule

- Initiation visit: Prior inclusion of first subject and pilot study
- Pilot study: within four weeks after ethics committee approval
- First subject in: immediately after pilot study is completed
- Monitor visit: after 3-6 subjects
- Last subject in: within nine months after including the first subject
- Last subject out: within four weeks after last subject is included
- Close-out visit: within four weeks after last subject out

5.4 Randomisation

One randomization list will be prepared containing 50 participants. The randomization list is dividing equally the number of participants for the VivaSight-DL group and the conventional reusable DLT group (standard care at the respective centre).

The randomisation list will be created by using the website random.org (https://www.random.org/lists/) and repeating the randomization three times. The treatment will be named 1 (=VivaSight-DL), 2 (=conventional DLT) in the list.

Sponsor will prepare envelopes according to the randomisation list. All envelopes will be clearly numbered in succession and the number will act as the subject number in the investigation. The Investigator will draw an envelope in successive order after the informed consent is obtained from the subject and a physician with experience in < 50 DLT placements in patients is assigned for the procedure. If additional subjects are to be included, the number of subjects must correspond to at least one block. Ambu will supply the additional envelopes.

6. TEST PARTICIPANTS

6.1 Inclusion criteria for subjects

- Oral explanation of the investigation and Patient Information has been given to the subject or legal representative
- The subject or legal representative has signed the Informed Consent
- The subject is admitted at OUH, department V, section BTY
- Subjects evaluated as eligible for single-lung ventilation with the use of a left sided DLT
- Subjects > 18 years of age

6.2 Exclusion criteria for subjects

- Subjects with known tracheobronchial anatomic anomalies
- Subjects going for emergency procedures
- Subjects with anticipated difficult airways
- Subjects with known tracheal pathology
- Subjects requiring rapid sequence induction
- Surgeries in which other lung isolation devices or techniques may be warranted (e.g. tracheostomy, nasal intubation, bronchial blockers)
- Subjects who cannot be intubated with a double-lumen tube (VivaSight-DL or conventional DLT)
- Subjects requiring a right-sided DLT
- Subjects who had participated in the study before

6.3 Inclusion criteria for physicians

- Physicians with experience in < 50 DLT intubations in patients
- Physicians who has completed the training course and has experienced at least 10 conventional DLT placements and three VivaSight-DL placements in manikin

6.4 Recruitment

The subjects included in this investigation will be under treatment in department V at OUH, and clinically judged by the investigator to be eligible for a single-lung ventilation. The subject, or if the subject is unable to, the subject's legal representative, will receive information orally and in writing about the investigation (see Patient Information, appendix I) from an Investigator (nurse or physician with at least two years of experience in anesthesia). Patient Information will be given in the pre-anaesthesia room, where the Investigator, the subject and the subjects relatives can discuss the study in privacy and undisturbed. If the subject agrees to participate they must sign the Informed Consent (see Informed Consent, appendix II) before start of the investigation.

A subject is considered included in the investigation as soon as informed consent has been signed. If subject or their legal representative do not consent to the investigation the procedure will be performed regardless, however off this investigation.

When a subject is included the Investigator assures that the subject meets all inclusion criteria and none of the exclusion criteria, by checking the relevant boxes in the CRF.

Participation in the investigation is voluntary and the subject or the subject's legal representative can at any time withdraw from the investigation without any consequence for further examinations and treatment.

If a subject withdraws from the investigation the subject will be replaced to ensure that the total number of subjects included in the analysis reach 50 subjects. If any data was recorded before withdrawal, this will be stored in the investigator binder but not used for analysis. When a subject is replaced the new subject is given a new subject number.

6.5 Exclusion during the examination

The subject can be excluded during the investigation if:

- The subject or legal representative decides to abort the study
- The subject is assigned to a physician with experience in > 50 DLT intubations in patients
- The investigator considers it necessary to change the type of endotracheal tube used for the procedure
- The investigator assess that it is necessary to exclude the subject from the investigation to ensure safety of the subject

If a subject withdraw from the study before the study randomization envelopes seal is broken (example no. 10), then the next subject will continue with consecutive subject number (no. 11).

If the subject is excluded *after* the procedure is started, he or she will be treated and receive routine treatment. Reason for exclusion will be stated in the CRF but otherwise data will not be collected in the CRF.

If the subject is excluded *before* the procedure is started, he or she will receive routine treatment. Reasons for exclusion will be stated in the CRF but otherwise data will not be collected in the CRF.

7. PROCEDURE

The participating site (OUH, department V, section BTY) will receive the protocol, 40 VivaSight-DL, two aView monitors and CRF's. The specific VivaSight-DL and aView lot numbers or the Shiley Lot numbers will be collected in the CRF under product identification.

All investigators must sign the Secrecy Agreement and the Investigator Sponsor Agreement before participating in the study. In addition, all investigators must provide an updated CV.

Before participating in the study, all novice physicians will complete a simulation training course and experience at least 10 conventional DLT placements and three VivaSight-DL placements in manikin. Investigational product training will be recorded on a separate form and stored in the Sponsor File along with Secrecy Agreements, Investigator Sponsor Agreements, CVs and documentation on the Investigators experience in intubation.

The investigation procedure will contain the following sections:

1. Recruitment of subjects
2. Preparation of procedure
3. Induction of anaesthesia
4. Intubation
5. Surgery
6. Subject monitoring during the surgery
7. Awakening of subject and follow up
8. Collection of cost data

Before the investigation is initiated all investigators will be instructed in the study protocol. Subjects will be recruited, and Informed Consent will be obtained by Investigators (nurses or physicians with at least two years of experience in anesthesia). The data will be collected on a CRF (paper or electronic format) during the procedure, when the CRF is completed the principal investigator will check that it is filled out correctly and sign it. Prior to the investigation a pilot will be run to test the data collection method in practice and ensure that the involved parts are familiar with the protocol (see section 7.1).

7.1 Pilot study

The purpose of the pilot study is to test the protocol in practice and ensure that the procedures allows for a proper data collection. After ethical approval up to 10 subjects will be recruited as described in section 6.3 and 12 for the pilot study. The first subject will be allocated to receive single-lung ventilation using Shiley™ Endobronchial Tube. The pilot will follow the same procedures as described in the subsequent sections (section 7.2-7.9). During the pilot, double data recording will be performed by two independent individuals (a physician and an investigator or a research assistant). The collected data will be compared across the two individuals to ensure that data collection is aligned. In case a significant difference in the recorded data is found, the cause of the variation is investigated, and the data collection method is corrected to ensure a standardized procedure. If the data collection procedure is corrected, the pilot is repeated until the data collection method for the Shiley™ Endobronchial Tube is verified. However, a maximum of 5 subjects are included. After completing the pilot testing of the Shiley™ Endobronchial Tube protocol, the VivaSight-DL protocol is verified following the same procedures. The data recorded during the pilot study will not be included in the data analysis.

7.2 Recruitment of subject

Patient Information will be given during the preoperative visit with the anesthesiologist prior to the surgery. Subjects will be recruited, and Informed Consent will be obtained as described in section 6.4 and 12. After signing the informed consent, the subject is enrolled in the study. The investigator who obtained Informed Consent will write his/her name under “Centre Identification” and “Investigators name” and collect the following demographic data, airway assessment parameters and surgical information’s in the CRF under “Patient Information”:

- Age
- Gender
- Height
- Weight
- ASA class
- Indication for the surgery
- Date of enrolment
- Fulfilment of the inclusion/exclusion criteria

7.3 Preparation of the procedure

Latest on the day of the procedure, the subject will be assigned a physician who will perform the intubation. If the subject is assigned a physician with experience in > 50 DLT intubations in patients, the subject will be excluded from the study and receive the standard treatment. If the subject is assigned a physician with experience in < 50 DLT intubations, the subject will be randomized to receive single-lung ventilation using either VivaSight-DL (test group) or Shiley™ Endobronchial Tube (control group).

Before initiating the investigational procedure, the following information is recorded in the CRF:

- Investigator Name (under "Centre Identification")
- Product Identification:
  - For test group:
    - VivaSight-DL Lot. No
    - aView Lot No
    - FOB brand and model
  - For control group:
    - Shiley Lot No
    - FOB brand and model
- Date of surgery (under "Data collection")
- Type of surgery performed (under "Data collection")

All equipment and all drugs needed for the entire procedure (anesthesia, intubation, surgery) is prepared and ready for use before anesthesia. In addition, a preparation table is set up in the operating room. The table will include the equipment needed for the intubation procedure, including:

- Puttable cloths
- Alcohol wipes
- Lubricant
- Antifogging agents
- Direct laryngoscope
- The intubation tube and accessories (e.g. adaptor, stylet and aView monitor for VivaSight-DL)
- Syringes

All essential equipment (e.g. laryngoscope handles, tubes) should have readily available back-up counterparts in case of unexpected failure. If anything is missing, it must be made available before the procedure is started.

The size of the double lumen tube is chosen prior preparation of the device. The ideal size of the tube result in a near-complete seal of the bronchial lumen without inflation of the cuff. After choosing the correct size, the device must be prepared following the manufacturer's instructions and the function of the device must be checked in advance, to ensure that the tube is working properly. If a tube has a malfunction, it must be replaced before starting the procedure. This information will be collected in the CRF and for the Ambu products a device deficiency (DD) form must be filled out. The following sections will describe in detail how the test device or the comparative device should be prepared.

7.3.1 Preparation of test device

The steps described below must be followed when preparing the test device

1. Connect VivaSight-DL to the single use adapter cable. Be careful to align the white arrow on the single use adapter cable with the green arrow on the VivaSight-DL tube round connector.
2. Connect the single use adapter cable to the aView™ monitor, be careful to align the arrow on the cable with the arrow indicator on the aView™ monitor. Verify that all electrical connections are stable and secure.
3. Press the power button on top of the aView™ monitor for at least one second until a live image appears. The aView™ user interface will be ready after approximately one minute, when the hourglass symbol disappears.
4. Check that the two LEDs at the tip of the tube are illuminated. If they are not illuminated, replace the tube.
5. Verify that there is a stable image on the aView™ monitor (projected from the tip of VivaSight-DL). Then turn off the monitor again until immediately prior to intubation.
6. Test the cuffs for integrity by inflating and deflating them completely.
7. Become familiar with the feel of the blue and clear pilot balloons.

7.3.2 Preparation of control device

The steps described below must be followed when preparing the comparative device

1. Carefully remove the sterile endobronchial tube from its protective package.
2. Test the cuffs, pilot balloons and valves of each tube by inflation prior to use: Insert a Luer tip syringe into each cuff inflation valve housing and inject enough air to fully inflate the cuffs
3. After test inflation of the cuffs, evacuate completely all the air from the cuffs and remove syringe
4. Examine and familiarize yourself with the Right Angle Swivel Connector assembly and Carlens adaptor before beginning the intubation procedure. After determining which connectors are required, firmly seat them into the extension circuit of the anesthesia machine.

7.4 Anesthesia

The subject will be pre-oxygenated by facemask for 3 minutes. Before pre-oxygenation the circle system must be filled with 100% oxygen. The flow of oxygen must be set at 10 liters to obtain the highest end tidal concentration of oxygen (EtO2).

When the subject is pre-oxygenated he or she will receive an intravenous infusion of propofol and Ultiva targeting the effect site. Muscle relaxant in the format of Esmeron. TOF value is monitored and complete relaxation needs to be confirmed prior to intubation. If biopsies and/or wedge resection is performed an intercostal block is given, for lobectomies an epidural is installed. Additionally, Fentanyl may be given if needed.

7.5 Intubation

For this study, "Intubation" is defined as the period from the direct laryngoscope is introduced into the subject's mouth until correct bronchial cuff placement is verified by capnography. The intubation is performed by a physician who fulfills the inclusion criteria and thereby is included in the study.

After anesthesia the table is adjusted to the physician performing the intubation. The is subject positioned on the back with the head bending backwards pointing up. In case of unanticipated difficult airways, the DAS 2015 guidelines is followed (9) and a trolley with all equipment needed for difficult airways will be available in the operating room within 60 seconds. The oral cavity and airway area is suctioned before inserting the DLT. It is important never to force the DLT into position. The specific intubation technique is described for VivaSight-DL and Shiley Endobronchial Tube in the following sections.

7.5.1 Intubation technique with VivaSigth-DL

1. Lubricate the tube (if needed), avoiding the area around the camera lens at the distal end of VivaSight-DL.
2. Introduce the direct laryngoscope into the subject's mouth
   - *Start recording the "Intubation time"*
3. VivaSight-DL is introduced into the subject's mouth
   - *A maximum of 3 intubation attempts, the number of intubation attempts are recorded in the CRF*
4. Advance the VivaSight-DL bronchial tube through the vocal cords with the tip facing upward and remove the stylet.
5. At the proximal portion of the tube, the bronchial arm of the tube will be positioned above the tracheal arm.
6. When the tip passes the vocal cords, and before the camera passes it, turn the tube 90 degress counterclockwise until the camera on the tube is facing up pointing towards the vocal cords. In this position, the tube passes through the vocal cords with the camera on the superior portion of the tube.
7. When the camera passes the vocal cords, advance the tube further until final positioning (2-3 cm above the main carina), without additional tube maneuvering. When the tube is in place, the proximal portion of the bronchial arm will be horizontal and on the left side.
   - *If any corrective actions are done to prevent repositioning of the tube after the cuffs are inflated it must be recorded in the CRF.*
8. Inflate tracheal cuff.
9. Remove the syringe from valve.
10. Promptly connect the tube to source of ventilation and confirm correct tube placement by capnography (CO_2 return)
11. Confirm correct tube position by looking at the aView monitor.
    - *If fiberoptic bronchoscopy is needed to confirm position, the number of times the fiberoptic bronchoscope (FOB) is used must be recorded in the CRF*:
      - Apply lubrication and antifogging agents to the FOB if needed.
      - The FOB is placed through the tracheal lumen.
      - The FOB is advanced, and the carina is identified.
      - The bronchial lumen of the tube must be visualized entering the left main stem bronchus.
12. The bronchial cuff is inflated under direct vision and should lie just distal to the carina.
    - *If the tube needs to be repositioned (bronchial cuff is deflated, and the tube is moved) it must be recorded in the CRF.*
      - *If fiberoptic bronchoscopy is needed to reconfirm position, the number of times the fiberoptic bronchoscope (FOB) is used must be recorded in the CRF*:

13. Confirm correct bronchial cuff placement by capnography (CO_2 return and SaO_2)
    - *Stop recording of the "Intubation time" and report it in the CRF.*
    - *Record the tracheal and bronchial cuff pressure in the CRF.*
    - *Record information on the intubation (Cormack-L classification, smooth intubation, need to bend the tube, resistance during tube placement, need of suction after tube placement)*
14. For deflation of one lung, open the corresponding tube lumen to room atmosphere prior to clamping the appropriate connecting tube.

7.5.2 Intubation technique with Shiley Endobronchial Tube

1. Lubricate the tube (if needed).
2. Introduce the direct laryngoscope into the subject's mouth
    - *Start recording the "Intubation time"*
3. Shiley Endobronchial Tube is introduced into the subject's mouth
    - *A maximum of 3 intubation attempts, the number of intubation attempts are recorded in the CRF*
4. Advance the Shiley Endobronchoal Tube through the vocal cords and remove the stylet
5. At the proximal portion of the tube, the bronchial arm of the tube will be positioned above the tracheal arm.
6. When the bronchial portion passes the vocal cords turn the tube 90 degress counterclockwise. In this position, the tube passes through the vocal cords.
7. Advance the tube further until final positioning (2-3 cm above the main carina), without additional tube maneuvering. After the tube has been properly positioned, the depth markings face in the cranial direction.
    - *If the tube if any corrective actions are done to prevent repositioning of the tube after the cuffs are inflated it must be recorded in the CRF.*
8. Inflate tracheal cuff.
9. Remove the syringe from valve.
10. Promptly connect the tube to source of ventilation and confirm tube placement by capnography (CO_2 return)
11. Apply lubrication and antifogging agents to the fiberoptic bronchoscope (FOB) if needed.
    - *The number of times the fiberoptic bronchoscope (FOB) is used must be recorded in the CRF*:
12. The FOB is placed through the tracheal lumen.
13. The FOB is advanced, and the carina is identified.
14. The bronchial lumen of the tube must be visualized entering the left main stem bronchus.
15. The bronchial cuff is inflated under direct vision and should lie just distal to the carina.
16. Confirm correct bronchial cuff placement by capnography (CO_2 return and SaO_2).
    - *Stop recording of the "Intubation time" and report it in the CRF.*
    - *Record information on the intubation (Cormack-L classification, smooth intubation, need to bend the tube, resistance during tube placement, need of suction after tube placement)*
17. For deflation of one lung, open the corresponding tube lumen to room atmosphere prior to clamping the appropriate connecting tube.

7.6 Surgery

For this study, "Surgery" is defined as period from correct bronchial cuff placement is verified by capnography until the DLT exits the subject's mouth. During the surgery, the physician who performed the intubation will monitor subject's respiration and ensure that the tube continues to be in the right position.

After intubation the subject is placed in a lateral position and prepared for surgery. When the repositioning is completed, the tube position is reconfirmed by continues view of the carina on the aView monitor (for VivaSight-DL) for the test group or by using a FOB for the control group.

- *When a fiberoptic bronchoscope (FOB) is used, it must be recorded in the CRF*:

During the surgery, validation that the system (VivaSight-DL or Shiley) is operating must be performed periodically by observing breathing movements. In addition, cuff pressure should be closely monitored and any deviation from the selected sealing pressure should be investigated and corrected immediately. For the test group (VivaSight-DL), the tube and the bronchial cuff position is continuously verified on the image at the aView monitor.

- *If cuff pressure is corrected to avoid repositioning of the tube, it must be recorded as a corrective action to prevent repositioning in the CRF.*

In case the needs to be repositioned during the surgery, *the number of times the tube is repositioned during the surgery must be recorded in the CRF*. If the tube needs to be repositioned, the subsequent steps should be followed:

1. Deflate the bronchial cuff unless lung separation is absolutely required during this time.
    - *Record whether the surgeon need to stop the procedure while the tube is repositioned in the CRF*.
    - *If the responsible anaesthesiologist is called for assistance to repositioning the tube it is recorded in the CRF*
2. Reposition the tube
3. Confirm correct tube position by looking at the aView monitor or with the use of FOB.
    - *If fiberoptic bronchoscopy is needed to confirm position, the number of times the fiberoptic bronchoscope (FOB) is used must be recorded in the CRF*:
        - Apply lubrication and antifogging agents to the FOB if needed.
        - The FOB is placed through the tracheal lumen.
        - The FOB is advanced, and the carina is identified.
        - The bronchial lumen of the tube must be visualized entering the left main stem bronchus.
4. The bronchial cuff is inflated under direct vision and should lie just distal to the carina.
5. Confirm correct bronchial cuff placement by capnography (CO_2 return and SaO_2)
    - *The time it takes to reposition the tube is recorded in the CRF (from syringe is attached to the valve to deflate the bronchial cuff until the bronchial cuff placement is confirmed)*.
    - *If the responsible anesthesiologist is called for assistance, the time from calling the responsible anaesthesiologist for backup until the tube is repositioned is recorded in the CRF*.

If a repositioning of the tube is prevented, *the number of times the repositioning is prevented must be recorded in the CRF*.

7.7 Subject monitoring during surgery

All subjects will be monitored continuously according to local routines, including pulse oximetry (SaO_2) and the arterial radialis pressure in arm of the non-surgical side, expired CO2, pressure/volume spirometry, a peripheral intravenous access and electrocardiography (ECG).

7.8 Extubation

Prior extubation of the subject, the tracheal and endobronchial cuffs is deflated completely by inserting a syringe into valve housing and removing the gas mixture, until a definite vacuum is noted in the syringe and the pilot balloon collapsed. The extubation is performed slowly.

- *Information about the extubation must be recorded in the CRF (smooth extubation, did the subject cough, did the subject complain of throat pain)*.
- *General information (adverse events, complications, deviations from protocol) about the procedure must be recorded in the CRF after extubation is completed.*

For the test group, the single use adaptor cable is disconnected from the aView monitor after extubation, and the aView monitor is turned off by pressing the power button for at least two seconds. The DLT (VivaSight-DL or Shiley) and single-use accessories are discarded after use.

7.9 Awakening of subject and follow up

Immediately after the surgery, the physician is asked to complete a questionnaire regarding the procedure just performed (Appendix VI).

All subjects are woken up immediately after surgery. Within forty-eight hours after the surgery, the subject will be contacted (in the hospital room or over the phone) by a research assistant who will ask questions regarding the subject's health-related life quality and potential side effects from the intubation (Appendix V). It will be the same research assistant who contacts all subjects in order to ensure identical data collection across subjects.

7.10 Collection of cost data

To enable an exact cost-model of single-lung ventilation, it is necessary to fully understand all processes related to the procedure. A research assistant will map all processes related to the procedure at the investigational site. Based on this, the research assistance collects all costs related to single-lung ventilation.

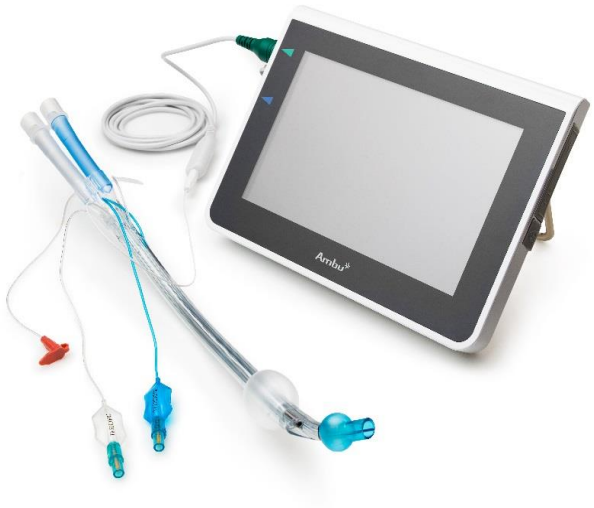
Resources and personnel time used for the individual processes will be tracked on a worksheet based on the initial mapping of the processes related to single-lung ventilation. This includes but is not excluded to personnel cost, procedure times, utilities, single-use equipment and capital equipment used during single-lung ventilation. Furthermore, all resources and times related to bronchoscopes will be collected via following at least 5 bronchoscopes from storage/drying cabinets through procedure, cleaning, reprocessing and back to storage/drying cabinets.

The following cost data will be collected via the investigational sites own records: Capital cost, repair costs, maintenance cost, cost of service agreements, cleaning verification costs, audit costs, personnel costs, cost of single-use equipment, administrative costs, cost of utilities and detergents. Note that if additional related costs are detected during the study they will be included in the cost-model.

8. MATERIALS

8.1 Test device

8.1.1 General information and device description



VivaSight-DL is manufactured by ETView Ltd (Catom 2 Street, Misgav Business Park, M.P. Misgav 2017900, Isreal), and is a sterile single-use, left sided, double-lumen cuffed PVC endobronchial tube with an embedded video imaging device and light source at the distal end of the tracheal lumen, and an integrated single use video/power cable (adapter cable) with connector.

VivaSight-DL displays images of the airway onto the Ambu® aView™ monitor (Ambu A/S, Baltorpbakken 13, 2750 Ballerup, Denmark) for as long as the device remains in place during intubation. VivaSight-DL has two color-coded low-pressure cuffs with corresponding pilot balloons. Additionally, for cleaning the imaging lens, the VivaSight-DL has an injection port leading to two lumens along the tube's wall, which opens at the distal end of the imaging lens. The VivaSight-DL System is intended to isolate the left or right lung of a patient for intensive care or surgery, one lung ventilation or one lung anesthesia.

The VivaSight-DL is CE-marked (CE 0483) and thereby approved for sale in Europe. It comes in four sizes as specified in the table below.

	35 Fr Left	37 Fr Left	39 Fr Left	41 Fr Left
Size	35 Fr	37 Fr	39 Fr	41 Fr
ID (mm)	4.0	4.2	4.8	5.0
OD (mm)	10.5	11.5	11.5	12.0
Length (+2/omm)	330	330	330	330

All VivaSight materials that are in contact with the patient, have been tested for biocompatibility with reference to ISO 10993 (10), current version.

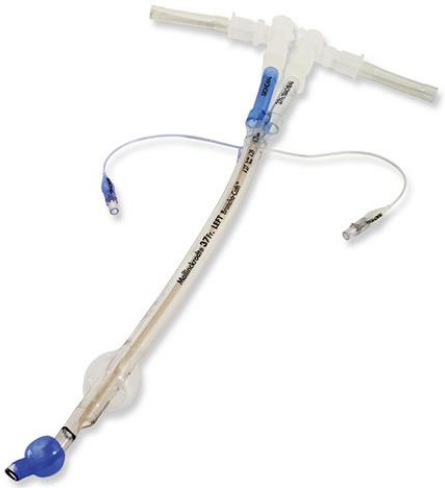
8.1.2 Precaution and handling

The system must not be used if, in the opinion of a qualified physician, such an application would endanger the patient or if the system as such or the method is contraindicated. Such cases will not be considered as part of the study.

The Ambu® VivaSight system must be used by doctors and nurses trained in single lung ventilation and handled according to the Instructions for use (IFU).

8.2 Comparative device

8.2.1 General information and device description



The Shiley endobronchial tube is manufactured by Covidien Ilc. (15 Hampshire Street, Mansfield, MA 02048, USA) and is a sterile single-use endobronchial tube with a left or right Bronch-Cath™ option, depending on the lung that needs to be ventilated. The tube features a low pressure tracheal and bronchial cuff to minimize risk of mucosal damage. The specially designed bronchial cuff assists with location of the distal tip when verification is confirmed by a fiber-optic bronchoscope. There is a slight curve at the distal tip to assist with placement. There is also an x-ray opaque carinal hook for confirming placement.

The Shiley endobronchial tube is CE marked (CE 0123) and thereby approved for sale in Europe. The sizes that will be used in this study is specified in the table below.

	35 Fr Left	37 Fr Left	39 Fr Left	41 Fr Left
Size	35 Fr	37 Fr	39 Fr	41 Fr
ID (mm)	4.8	5.1	5.3	5.4
OD (mm)	11.7	12.3	13	13.7

8.3 Supplementary materials and equipment

In addition to the test device and the comparative device, the following equipment will be available for use during the procedure:

- Direct laryngoscope
- Suction catheter
- Pentax FI-10BS (Pentax, USA)
- Olympus LF-V (Olympus, Japan)

8.4 Investigator's Brochure

As the devices are approved for sale (CE-marked), an Investigator's Brochure is not required. The IFU will be available in the packaging of the devices.

8.5 Device Accountability and Traceability.

The sites included in the study will make their conventional bronchoscopes available as comparator for this investigation.

The site will free of charge receive 40 Ambu® VivaSight-DL devices. For this study two Ambu® aView™ monitors will be provided as well. Any devices remaining after the end of the study will be accounted for and shall be returned to Ambu®.

There are no requirements regarding device accountability for CE marked devices. However, for logistical reasons the Sponsor will account for all devices delivered to and returned from the Investigators in a Device Accountability Form kept at Sponsor's address.

9. MONITORING

During the period of the study, a representative of the Sponsor will act as monitor of the study. The Investigator may contact Sponsor representatives, as listed on page 3, at any time.

9.1 Monitoring Visits

During the period of the investigation a representative of the sponsor will perform an initiation visit, monitor visits and close out visits on site or per distance.

- Initiation Visit: This meeting will be held before the study is initiated, and the aim of this meeting is to train the investigators and research assistants on the investigation procedure, perform a page-by-page revision of the protocol with emphasis on reporting of deviations, adverse events and how to complete the CRF. Moreover, contract signature and approvals from authorities will be verified, and monitoring arrangements will be discussed. It is required that *all* investigators participating are present in this meeting.

- Routine Visit: The aim of these monitoring visits is to corroborate the study progress and perform source data verification. CRF will be monitored for completeness and correctness of the data. It is required that at least one investigator is available during monitoring visits. A monitor visit will be done at each of the investigation site after 3-6 subjects completing the study.

- Close-out visit: The aim of this meeting is to close financial aspects, check that all essential documents are complete and up to date, all outstanding queries are resolved, current state of all adverse events is documented, arrangement for achieving all study documentation, device accountability, collection of the original CFR, and notification of the corresponding authorities. This meeting will be conducted after the last subject has been completed or no later than three months after finishing the data collection.

The monitor is responsible for planning the monitoring visit

9.2 Source Data Verification

The Case Report Form, Informed consent, and Patient Registration List will be verified against the subject's medical record for the following parameters:

- Subject identification
- Reason for hospitalization
- Inclusion/exclusion criteria
- Adverse events
- Completion/Drop out
- Subject's participation in the investigation

Data verification will be done for 20% of the subjects participating in the study. If any inconsistencies is found between study data and the medical record, data verification will be performed for all subjects.

10. AUDIT

Audit of the clinical investigation may be conducted by the Sponsor or third parties designated by the sponsor to evaluate compliance with the CIP, written procedures and International Standards (6). These audits may cover all involved parties, systems and facilities and are independent from routine monitoring. The aims of the audit are:

- to assess the effectiveness of the monitoring,
- whenever there are repetitive deviations from the CIP,
- to prepare the investigation for a regulatory inspection,
- when requested by a regulatory authority, etc.

Audits may be performed during the investigation. All parties will be informed in advance of the date and objective of the audit.

11. CLINICAL INVESTIGATION PLAN

The CIP was made according to the Council Directive 93/42 EEC of 14 June 1993 and amendment 2007/47/EC (5), the guidelines set out in ISO 14155 (6), ISO 14971 (7), and the Helsinki Declaration (8).

An example of the Case Report Form is enclosed in the CIP together with the Patient Information and Informed Consent. The Case Report Form is in English and should be filled in English when possible. Missing data not recorded on the day of the procedure should be filled in later accompanied by date and signature. Data that are evaluated as incorrect by Investigator should be crossed over with ink allowing the "old data" to be seen ~~(example)~~. The Investigator shall then write the new and correct data and then sign and date.

Any discrepancies compared to the procedures described in this CIP shall be documented and reported to the Sponsor or monitoring person.

The Sponsor and the Investigator must sign the CIP before the investigation can start at the centre.

11.1 Patient Registration List

The Patient Registration List is a centre specific document that links each subject to a subject number given by the Investigator. The form is pre-printed with ranked numbers. The Investigator will fill in the subject name, birth date and date for subject enrolment and inclusion into the investigation. The list must not leave the Investigator site. The list will be verified during monitoring or at the final visit.

12. SUBJECT DOCUMENTS

12.1 Patient Information

The Patient Information (appendix I) is a brief summary of the investigation written in a language understandable for the subject. The Patient Information describes the aim of the investigation, benefits and risks to the subject and the possibility of compensation. Furthermore, it includes an explanation of alternative methods and consequences of withdrawal from the investigation.

The Patient Information reflects current practice in device investigations and is provided according to European regulation, European Medical Directive (2007/47/EC) [1], DS/EN ISO 14155 [2] and Helsinki Declaration [3]. The Patient Information is enclosed in appendix I of this CIP.

The Investigator will review the patient information with each possible subject or legal representative and explain the investigation to him/her during the preparation meeting with the anesthesiologist prior to the surgery. The subject or legal representative will be given sufficient time to consider participation (minimum 30 minutes) and it is recommended that a witness from the patient side is present during the information procedure. Patient Information will be given in the pre-anaesthesia room, where the Investigator, the subject and the subjects relatives can discuss the study in privacy and undisturbed. If the subject requests more time to consider participation in the investigation the Investigator will schedule a new time to obtain Informed Consent. The Patient Information describes the contact details of the investigator.

12.2 Informed Consent

Informed Consent (appendix II) is the voluntary confirmation and documentation of the willingness of a subject to participate in a particular investigation, after information has been given orally and in writing to the subject. Point of enrolment is from the time when informed consent is signed. The subject and Investigator must each sign and date the Informed Consent. The subject can be excluded from the study after Informed Consent is obtained in if the subject is assigned a physician with experience in > 50 DLT intubations in patients. This is done, as the subject is not assigned a physician until earliest the day before the surgery. To ensure that the subject has sufficient time to consider participation the Patient Information is given at the preparation meeting which can take place before a physician is assigned.

The Investigator signs to confirm that information has been given to the subject. One copy is for the subject and the other one for the Investigator binder.

A draft version of the Informed Consent is attached to the CIP. A final copy of this Informed Consent must be provided to the Sponsor prior to first use.

Participation in the investigation is voluntary and the subject can at any time chose to be withdrawn from the investigation. This will not have consequences on his/her treatment.

13. ADVERSE EVENTS

13.1 Definitions

The risks associated to the used of the device have been estimated in an Ambu Product Risk Evaluation following ISO 14971 (7). The residual risks as identified in the risk evaluation, as well as the risks to the subject associated with the procedures of the clinical investigation are balanced against the anticipated direct or indirect benefits for the patient.

Adverse Device Effect (ADE):
Adverse event relates to the use of an investigational medical device, including events resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This also includes events resulting from a use error or intentional misuse.

Adverse Event (AE):

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs in subjects, users or other persons whether or not related to the investigational medical device.

NOTE 1: This includes events related to the investigational device or the comparator.
NOTE 2: This includes events related to the procedures of the clinical investigation.
NOTE 3: For users or other persons this is restricted to events related to the investigational medical device.

Device deficiency (DD):
Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

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

Serious Adverse Event (SAE):
Adverse event that:

a) led to a death,
b) led to a serious deterioration in health that either:
   1) resulted in a life-threatening illness or injury, or
   2) resulted in a permanent impairment of a body structure or a body function, or
   3) required in-patient hospitalization or prolongation of existing hospitalization, or
   4) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

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

NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

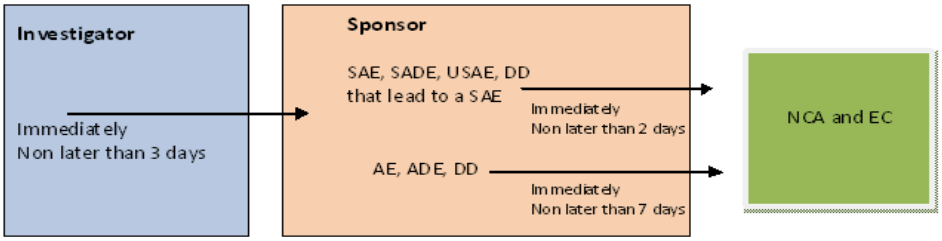
13.2 Investigator requirements

Investigator must record and document all adverse events in the Adverse Event Form.

All Adverse Events shall be reported to the Sponsor within three calendar days.

Note that in this case the Investigator is only required to report to the Sponsor, and the Sponsor is responsible of reporting to the Ethics Committee and Competent Authority.

See table below:



Emergency contact details are stated on the form and are as follows:

Fax to AMBU A/S Fax no.: +45 (72 25 20 55)
Attn.: CLINICAL DEPATMENT and REGULATORY AFFAIRS DEPARTMENT

Anna Charlotte Lundgaard or Kristine Rasmussen
aclu@ambu.com or krra@ambu.com
+ 45 2964 3748 or + 45 7225 2222

After termination of the serious adverse event/adverse device effect a copy of all relevant medical documents must be sent to the Sponsor including the finalised Adverse Event Form.

13.3 Sponsor requirements

The Sponsor shall report all AE to the Competent Authorities and Ethics Committee with the following timelines (11):

- All serious adverse events (SAE, SADE, USAE, and DD that may lead to a SAE) must be reported to the Sponsor immediately – no later than two calendar days.
- All AE, ADE and DD shall be informed to the sponsor immediately - within seven calendar days after occurrence.

13.4 Expected clinical occurrences

The risks associated to the use of the device have been estimated in the Ambu Product Risk Evaluation following ISO 14971 (7). The residual risks as identified in the risk evaluation, as well as the risks to the subject associated with the procedures of the clinical investigation are balanced against the anticipated direct or indirect benefits for the patient.

The clinical benefit from using the VivaSight-DL is continues monitoring of tube position throughout the surgical procedure thus the need of a bronchoscope to confirm tube position can be reduced. Based on these conditions the process can be optimized without compromising patient safety.

14. EARLY INTERRUPTION OF THE INVESTIGATION

The Sponsor, Investigator, Regulatory Authority or Ethics Committee may decide to interrupt the investigation in case of detecting repetitive serious adverse events, in case of unexpectedly poor performance of the device, repetitive major deviations from the protocol, etc.

In case of early interruption of the clinical investigation, subjects still in the investigation will be called for a final examination.

15. DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN

The investigator shall record any deviation from the CIP in the CRF together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance.

When relevant, the Sponsor shall inform the ethics committee, competent authorities or the appropriate regulatory bodies of the deviations. Deviations should be reviewed to determine the need to amend the CIP or terminate the investigation.

16. RESPONSIBILITIES

The Sponsor is responsible for the investigation as described in the European Standard DS/EN ISO 14155 (6), the MDD Council Directive 93/42/EEC of 14 June 1993 and amendment 2007/47/EC (5).

The monitor of Ambu A/S is responsible for monitoring the investigation as described in section 8 and in compliance with the European Standard DS/EN ISO 14155 (6).

The clinical Investigators are responsible for conducting the investigation as described in the Clinical Investigation Plan, Sponsor-Investigator Agreement (CLI-000424), according to the Helsinki Declaration (8) and ISO 14155 (6).

17. INSURANCE

Ambu A/S will within the limitations of their legal responsibility, accept responsibility for any damage suffered by a subject as a result of using the test products in the clinical investigation as described in this CIP. Ambu A/S is insured in the insurance company IF Skadeforsikring and all subjects will be fully covered throughout the investigation. For further details please see the Investigator Sponsor Agreement (CLI-000424).

18. DATA MANAGEMENT AND STATISTICAL ANALYSIS

18.1 Sample size

The following formula is used to validate that the chosen sample size is sufficient to detect an effect on the primary outcome):

$$n_1 \geq \left(\frac{(\sigma^2_{DLT} + \sigma^2_{vivasight}) * (\lambda_z + \lambda_\beta)^2}{(\bar{x}_{DLT} - \bar{x}_{Vivasight})^2} \right)$$

Combined standard deviation and grand mean are based on three studies (2,12,13).

$\bar{x}_{DLT} = 0{,}37234$ *bronchoscopes used to correct DLT placement*
$\bar{x}_{vivasight} = 0{,}01087$ *bronchoscopes used to correct vDLT placement*
$\sigma^2_{DLT} = 0{,}23622$ *bronchoscopes*
$\sigma^2_{vivasight} = 0{,}01087$ bronchoscopes

We set power to 90% thus the $\lambda_\beta = 1.28$ and significance level at 5% → $\frac{0{,}05}{2} = 0{,}025 \rightarrow \lambda_z = 1{,}96$
Thereby, to reject the H_0 the sample size must be:

$$n_1 \geq \left(\frac{(0{,}23622 + 0{,}01087) * (1{,}96 + 1.28)^2}{(0{,}37234 - 0{,}01087)^2} \right) = 19{,}852 \text{ patients}$$

$$N = 19{,}852 * 2 = 39{,}7035 \rightarrow 40 \text{ patients}$$

Therefore, a total sample size (N) of 40 generates a power of 90%. A sample size of 50 patients allows a potential dropout rate of 20 percent.

18.2 Data management

Case report forms will be completed on paper or electronically and a copy will be stored on site. If data is recorded on a paper format of the CRF, two individuals at Ambu A/S will perform double data entry when the study is terminated. Any unclear data points will be highlighted in a Data Clarification Form that will be sent to the responsible investigator for clarification. An error list will be generated, and errors corrected by Ambu A/S staff. All data will be analysed internally at Ambu A/S.

18.3 Statistical analyses

18.3.1 General aspects

Descriptive statistics, i.e. number of subjects, mean, standard error of mean (S.E.M), 95% CI will be presented for continuous data. Categorical data will be summarized using frequency tables (frequency and percent).

18.3.2 Handling of dropouts and missing data

Data from intermediate dropouts, who has been intubated but not undergone surgery will not be included within the analysis of the primary outcome. Furthermore, data from intermediate dropouts will be included until dropout. Early dropouts, who dropout prior to intubation will be excluded from all analysis.
Potential missing data points will be explored and substituted via regression imputation or listwise deletion as appropriate. Using substitutions via regression imputation the existing variables are used to make predictions for the missing values. As a result, the data is retained, and significant altering of the standard deviation is avoided. To examine whether potential missing data points are missing at random, or whether they could lead to a potential bias, an independent sample t-test will be applied, comparing the remaining variables of the observations with full data and the observations with missing data.

18.3.3 Method of statistical analysis in relation to objectives

Primary outcome:

- Number of times where fiberoptic confirmation of tube position during intubation or surgery is needed

  If the observations are normally distributed, a student t-test will be used to examine if number of times the tube position needs to be verified with a bronschoscope is significantly different for procedures using VivaSight-DLT compared to a conventional DLT. If the observations are not normally distributed, a Mann-Whitney U test will be used.

Secondary outcomes:

- Intubation time (sec)
  - If the observations are normally distributed, a student t-test will be used to examine if intubation time (sec) is significantly different for procedures using VivaSight-DLT compared to a conventional DLT. If the data is not normally distributed, transformation will be attempted to normalize the data. If the observations are still not normally distributed, a Mann-Whitney U test will be used.
- Number of intubation attempts
  - If the observations are normally distributed, a student t-test will be used to examine if number of intubation attempts is significantly different for procedures using VivaSight-DLT compared to a conventional DLT. If the observations are not normally distributed, a Mann-Whitney U test will be used.
- Number of times incorrect placement of the tube is prevented during intubation
  - If the observations are normally distributed, a student t-test will be used to examine if number of intubation attempts is significantly different for procedures using VivaSight-DLT compared to a conventional DLT. If the observations are not normally distributed, a Mann-Whitney U test will be used.
- Number of times the tube needs to be repositioned during intubation
  - If the observations are normally distributed, a student t-test will be used to examine if number of times the surgeon asked the tube placement to be confirmed is significantly different for procedures using VivaSight-DLT compared to a conventional DLT. If the observations are not normally distributed, a Mann-Whitney U test will be used.
- Number of times where the physician prevents repositioning of the tube during surgery
  - If the observations are normally distributed, a student t-test will be used to examine if number of intubation attempts is significantly different for procedures using VivaSight-DLT compared to a conventional DLT. If the observations are not normally distributed, a Mann-Whitney U test will be used.
- Number of times the tube needs to be repositioned during surgery
  - If the observations are normally distributed, a student t-test will be used to examine if number of times the surgeon asked the tube placement to be confirmed is significantly different for procedures using VivaSight-DLT compared to a conventional DLT. If the observations are not normally distributed, a Mann-Whitney U test will be used.
- Repositioning time (seconds) during surgery
  - If the observations are normally distributed, a student t-test will be used to examine if time used to reposition the tube is significantly different for procedures using VivaSight-DLT compared to a conventional DLT. If the data is not normally distributed, transformation will be attempted to normalize the data. If the observations are still not normally distributed, a Mann-Whitney U test will be used.
- Number of times the surgeon stops working while the tube is repositioned
  - If the observations are normally distributed, a student t-test will be used to examine if number of times the surgeon asked the tube placement to be confirmed is significantly different for procedures using VivaSight-DLT compared to a conventional DLT. If the observations are not normally distributed, a Mann-Whitney U test will be used.
- Time the backup anesthesiologist spends on the procedure
  - If the observations are normally distributed, a student t-test will be used to examine if time used to reposition the tube is significantly different for procedures using VivaSight-DLT compared to a conventional DLT. If the data is not normally distributed, transformation will be attempted to

normalize the data. If the observations are still not normally distributed, a Mann-Whitney U test will be used.

Tertiary end-points

- Qualitative measures (questions to the patient)
  - Any side effects from the surgery: Data will be summarized using frequency tables and examined via regression model as suitable.
  - Daily function level prior surgeryPostoperative scores will be summarized in a frequency table and examined via regression model as suitable.
- Qualitative measures (questions to the person who intubated)
  - Ease of tube placement (on a scale from 1=very easy to 5=very difficult)
  - How would you rate the overall perception of quality and functionality of the tube (DLT or VivaSight)? (Very poor, poor, acceptable, good, very good)
  - Would you prefer to use this method for single lung ventilation in the future? (yes/no)
    A Chi-sqaure test will be applied to examine whether qualitative measures are significantly different for procedures using VivaSight-DLT compared to a conventional DLT.

18.3.4 Level of significance and handling of multiplicity

All statistical tests will be two-sided and will be performed at the significance level (α) of 5%.
To account for the explorative analysis', a Bonferroni correction is used.

18.3.5 Interim analysis

No interim analysis will be conducted as all medical devices utilized are CE marked and suitable for performing the test procedures. Additionally, the sample size is relatively small and the time horizon correspondingly short.

18.4 Deviations from the Statistical Plan

It is unlikely that the statistical plan will change during the short trial period since the interim analysis is excluded. Any deviations in the statistical plan will be reported in the final study report.

18.5 Pass/fail criteria

All patients included in the results must fulfill the inclusion and exclusion criterion.

Primary outcome:

- Number of times the tube position needs to be verified with a scope.
  Must be stated in integers.

Secondary outcomes:

- Intubation time (seconds)
  - There must be a time difference between the DLT entering the patient and the correct DLT positioning is verified. Must be stated in seconds.
- Number of intubation attempts
  - Must be stated in integers.
- Number of times incorrect placement of the tube is prevented during intubation
  - Must be stated in integers.
- Number of times the tube needs to be repositioned during intubation
  - Must be stated in integers
- Number of times where the physician prevents repositioning of the tube during surgery
  - Must be stated in integers.
- Number of times the tube needs to be repositioned during surgery
  - Must be stated in integers and the reposition time must be positive in cases where repositioning has been reported
- Reposition time (seconds) during surgery
  - The time must be positive in cases where that the tube has been repositioned.
- Number of times the surgeon stops working while the tube is repositioned

- Must be stated in integers, reposition time must be positive and in must be reported that a tube needs to be repositioned
- Number of times the backup anesthesiologist is called into the operating room for assistance
  - Must be stated in integers
- Time the back-up anesthesiologist spends on the procedure
  - No predetermined pass/fail criterion

Tertiary end-point

- Qualitative measures (questions to the patient)
- Qualitative measures (questions to the person who intubated)
- No predetermined pass/fail criterion

18.6 Data file

Copies of CRFs, Patient Registration List, and informed consents will be kept on the investigation site in accordance with local regulations or at least for a period of 5 years after the investigator has signed the final Investigation report. Moreover, the investigator site file is filed accordingly. Ambu will file the original CRFs for the rest of the products' lifetime + 5 years. Moreover, Adverse Event Forms, Statistical Analysis, agreements, approvals, Investigators' CVs, CIP, and CIR will also be filed.

18.7 Health economic evaluation

The cost of all relevant processes related to single-lung ventilation will be summed and the average cost per procedure will create the cost input into a cost-effectiveness model. Capital costs will be discounted at the national appropriate discount rate of 4.05 and depreciated over the assumed life span of the device (14).
The effects measures included in the cost-effectiveness model includes:

- The primary outcome: the risk of needing a bronchoscope to check DLT placement
- The subsequent risk of cross-infection due to bronchoscopy. This risk is calculated based on current evidence from the literature

Cost-effectiveness data will be analyzed as a base-case result via a decision tree running over a short time period of one year within the hospital setting where the procedure is taking place. This will result in the deterministic ICER.
The cost data, risks and base-case will be presented in a table.
To challenge the base-case robustness several 1-way deterministic sensitivity analyses will be conducted. Doing so, major contributors to the base-case result will be varied to test their contribution to the base-case. The one-way sensitivity results will be presented as a tornado plot. To validate the overall robustness and second order uncertainty of the base-case a probabilistic sensitivity analysis will be conducted. Here, all the stochastic variables contributing to the ICER will be varied simultaneously. The probabilistic sensitivity analysis will be presented in a cost-effectiveness plane.

19. INVESTIGATOR – SPONSOR COOPERATION

19.1 Investigator-Sponsor Agreement

A written agreement is made between the Principal Investigator, Investigation site and the Sponsor and shall be signed before start of the clinical investigation. The agreement describes the responsibility and liability for Sponsor and Investigator respectively, during the investigation.

19.2 Clinical Investigation Report

The Clinical Investigation Report will be prepared according to EN/ISO 14155 (6) by the Sponsor. The Sponsor has one month to finalise the Clinical Investigation Report after receipt of the final statistical report. The involved Investigators have two weeks to comment on and approve the final report. All Investigators and the Sponsor are required to sign the report. If an Investigator does not sign the final report, a justification shall be provided.

19.3 Publication/Presentations

All information supplied by Ambu A/S to the Investigator in connection with this investigation shall remain the sole property of Ambu A/S and is to be considered confidential information. No confidential information shall be disclosed to others without prior written consent from Ambu A/S.

The clinical study will be registered on a public accessible database before recruitment of the first subject, e.g. https://clinicaltrials.gov/. A summary of the results of the investigation will be published in the same public accessible database. The subjects' identity will remain confidential.

A publication shall be prepared and submitted two months after approval (signature) of the CIR. The publication will be written by Sara Larsen from Aalborg University (first author) in cooperation with her internal supervisor at Aalborg University and Principal Investigator (last author). The Principal Investigator is responsible of pointing out any other involved investigators who should be involved in and named on the publication. The publication shall be submitted to a relevant scientific journal. Sponsor and Investigators have two weeks to comment on the draft before submission. If no comments have been received after two weeks, the submission will proceed.

If the publication has not been submitted on the agreed time plan, the Sponsor can prepare a manuscript for commercial use on the basis of the investigation or even a publication based on the study results. The Principal Investigator and other involved Investigators have the right to comment on the manuscript within two weeks. If no comments have been received after two weeks the Sponsor may proceed with the manuscript.

In the event of any disagreement in the content of a publication, the opinion of the Investigators and Ambu will be fairly represented in the publication.

The Investigators have also the right to present the results at a relevant international meeting. Sponsor and Investigators have two weeks to comment on the draft presentation. If no comments have been received after two weeks the submission will proceed.

A list of relevant conventions including deadlines for poster submissions and relevant medical journals for the final publication may be considered and written as a publication strategy.

20. ETHICAL CONSIDERATIONS

The clinical investigation will be conducted in accordance with The Declaration of Helsinki (8).

20.1 Subject information and consent

Written informed consent will be obtained from all subjects, or their legal representative, participating in the investigation after thorough written and verbal information given by the Investigator or his/her representative. Each subject will be fully informed about the aim of the investigation, procedures, potential risks or inconveniences and expected benefits. The test participants will be informed that their participation is voluntary and that they may leave the investigation at any time without giving any reason and without this having any influence on their treatment. (See appendix I).

20.2 Ethics Committee/Institutional Review Board (IRB)

The CIP and other relevant documents will be submitted to the appropriate Ethics Committee and their approval or written opinion will be obtained before commencement of the investigation. Any amendment to the CIP will be submitted to the same Ethics Committee.

20.3 Data protection

All subject data will be handled according to the Danish law for treatment of personal information, Law no. 429 of May 31, 2000 as amended by law no. 280 of April 25, 2001.

All subject data collected during the course of this investigation will be kept strictly confidential. An investigation number will identify subjects and the monitor will have limited access to subject's files/documentation for source data verification. Any information, which could identify a subject, will remain with the Investigator where it will be filed with investigation documents. Subjects will remain anonymous for data analysis.

Should the investigation require future review, it may be necessary to allow limited access to regulatory authorities for audit purpose only.

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APPENDIX V: CASE REPORT FORM

Case Report Form – Comparison of VivaSight-DL and Conventional DLT

Centre Identification	
Hospital name	Odense University Hospital
Department	Department V – Unit BTY
Investigators name	

Principal investigator signs when Case Report Form has been completed:

Date:	Signature:

Subject Information			
Subject number:		**Date of enrolment** (DD-MM-YYYY)	

Demographics			
Sex	☐ Female ☐ Male	**Height**	cm
Age	years	**Weight**	kg
Indication		**ASA Class**	☐ I ☐ II ☐ III ☐ IV

Inclusion (all questions must be answered "Yes" for the patient to be included)	**Yes**	**No**
Oral explanation of the investigation and Patient Information given		
Informed Consent obtained		
Clinical identification for single-lung ventilation during proposed surgery		
The subject is admitted to department V at OUH		
The subject is ≥ 18 years		
Exclusion (all questions must be answered "No" for the patient to be included)	**Yes**	**No**
Previously participated in the investigation		
Emergency procedure		
Known tracheobronchial anatomic anomalies		
Anticipated difficult airways		
Requiring rapid sequence induction		
Surgeries in which other lung isolation devices or techniques may be warranted (tracheostomy, nasal intubation)		
Intubation not possible using DLT (VivaSight or conventional)		
Subject requires a right-sided conventional DLT or VivaSight-DL		

Document Identification for Subject Questionnaire:

Physician Information	
Physicians name:	

Inclusion (all questions must be answered "Yes" for the physician to be included)	**Yes**	**No**
Physician has with experience in < 50 DLT intubations in patients		
Physicians who has completed the simulation training course and has experienced at least 10 conventional DLT placements and three VivaSight-DLT placements in manikin		
Physician has given consent to use personal information		

Document Identification for Physician Questionnaire:_____

Case Report Form – Comparison of VivaSight-DL and Conventional DLT

Product Information

Subject is randomized to:	☐ Test group (VivaSight-DL)	☐ Control group (Shiley)

Product information should only be filled out for the products being used.

Tube information	
Lot. No:	
Size (Fr)	☐ 35 ☐ 37 ☐ 39 ☐ 41

aView monitor information (only applies for the test group)	
Lot. No:	

Supplementary products	Brand	Model	Additional information
Direct laryngoscope			
FOB			

Data collection

Type of surgery		Date of surgery	Knife start (hh:mm)	Knife end (hh:mm)
☐ Open	☐ Keyhole			

Intubation (the period from the direct laryngoscope is introduced into the subject's mouth until correct bronchial cuff placement is verified by capnography)

Bronchoscope use (n)	Repositioning prevented (n)	Tube repositioned (n)	Intubation attempts (n)	Intubation time (sec)
				sec.

Cormack-L classification	Smooth intubation?	Need to bend tube?	Resistance during tube placement?	Need of suction after tube placement?
☐ 1 ☐ 2 ☐ 3 ☐ 4	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

Bronchial cuff pressure	Tracheal cuff pressure	Comments:
Cm H_2O	Cm H_2O	

Surgery (the period from correct bronchial cuff placement is verified by capnography until the DLT exits the subject's mouth)

Bronchoscope use (n)	Repositioning prevented (n)	Tube repositioned (n)

Repositioning of tube	Time used to reposition the tube	Rate of restriction on the surgical procedure	Responsible anesthesiologist assisted	Time spend by responsible anesthesiologist
1st repositioning	sec	☐ Not restricted ☐ Restricted ☐ Completely restricted	☐ Yes ☐ No	sec
2nd repositioning	sec	☐ Not restricted ☐ Restricted ☐ Completely restricted	☐ Yes ☐ No	sec
3rd repositioning	sec	☐ Not restricted ☐ Restricted ☐ Completely restricted	☐ Yes ☐ No	sec

Extubation of the subject	Smooth extubation?	Did the subject cough?	Did the subject complain of throat pain?
	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

Comments:

Any adverse events/adverse device effects?		
Yes	No	If yes: please specify (if SAE or SADE please fill out SEA or SADE form):

Any complications in relation to airway management?		
Yes	No	If yes: please specify:

Any general complications?		
Yes	No	If yes: please specify:

Any deviations from the Investigation protocol?		
Yes	No	If yes, please specify:

Were more devices than expected used (>1)?		
Yes	No	If yes, please specify why and the number of devices used:

APPENDIX VI: QUESTIONAIRE FOR SUBJECTS

Spørgeskema omhandlende helbredsrelateret livskvalitet og bivirkninger efter operation i hjerte-lunge området

I forbindelse med at De har deltaget i et forskningsstudie og har fået foretaget en operation med behov sikring af dine luftvejene på Odense universitetshospital, vil vi bede Dem besvare nedenstående spørgeskema omhandlende din generelle helbredsrelaterede livskvalitet samt eventuelle bivirkninger efter din operation.

Forsøgsperson nummer: _____ **Dato for udfyldelse:**_____ **Tidspunkt for udfyldelse:**_____

Spørgsmål omhandlende helbredsrelaterede livskvalitet						Kommentarer
Hvordan vil De vurdere Deres overordnet livskvalitet indenfor de sidste 4 uger?	❑ Dårlig	❑ Mindre god	❑ God	❑ Meget god	❑ Fremragende	
I hvor høj grad har De haft smerter indenfor de sidste 4 uger?	❑ Slet ikke	❑ I mindre grad	❑ I nogen grad	❑ I høj grad	❑ I meget høj grad	
I hvor høj grad har Deres smerter påvirket Deres hverdag?	❑ Slet ikke	❑ I mindre grad	❑ I nogen grad	❑ I høj grad	❑ I meget høj grad	
I hvor høj grad har De følt dem ængstelig eller deprimeret indenfor de sidste 4 uger?	❑ Slet ikke	❑ I mindre grad	❑ I nogen grad	❑ I høj grad	❑ I meget høj grad	
Hvordan vil De vurdere Deres helbred alt i alt?	❑ Dårligt	❑ Mindre godt	❑ Godt	❑ Meget godt	❑ Fremragende	

Spørgsmål omhandlende eventuelle bivirkninger efter operationen						Kommentarer
Hvor mange timer er der gået siden Deres operation?	❑ 0-4	❑ 5-9	❑ 10-14	❑ 15-19	❑ Over 20	
Har De tidligere fået foretaget en lignende operation?	❑ Ja	❑ Nej				
Har De oplevet hoste efter Deres operation?	❑ Ja	❑ Nej				
Hvis ja, i hvor høj grad har De hostet?	❑ Mild	❑ Moderat	❑ Svær			
Har De oplevet hæshed efter Deres operation?	❑ Ja	❑ Nej				
Hvis ja, i hvor høj grad har De været hæs?	❑ Mild	❑ Moderat	❑ Svær			
Har De haft smerter i svælget efter Deres operation?	❑ Ja	❑ Nej				
Hvis ja, hvordan vil De beskrive Deres smerter?	❑ Milde	❑ Moderate	❑ Svære			

Hvis spørgeskema ikke besvares, begrundes dette her:	

APPENDIX VII: QUESTIONAIRE FOR PHYSICIANS

Name of physician:_____

Date of procedure:_____

Subject number of the subject on which the procedure was performed:_____

Physician Experience						**Comments**
How long have you practiced medicine?	❑ < 1 year	❑ 1-2 years	❑ 2-3 years	❑ 3-4 years	❑ > 4 years	
In total, how many single lumen tube placements have you performed in patients?	❑ 0-24	❑ 25-49	❑ 50-74	❑ 75-99	❑ ≥ 100	
Over the past three months, how many single lumen tube placements have you performed in patients?	❑ 0-24	❑ 25-49	❑ 50-74	❑ 75-99	❑ ≥ 100	
In total, how many conventional DLT placements have you performed in patients?	❑ 0-9	❑ 10-19	❑ 20-29	❑ 30-39	❑ 40-49	
In total, how many VivaSight-DL placements have you performed in patients?	❑ 0-9	❑ 10-19	❑ 20-29	❑ 30-39	❑ 40-49	

Ease of use						**Comments**
Which DLT did you use for this procedure?	❑ VivaSight-DL		❑ Conventional Bronchoscopy			
How would you rate easy of insertion?	❑ Very difficult	❑ Difficult	❑ Acceptable	❑ Easy	❑ Very easy	
How would you rate the overall perception of quality and functionality of the DLT used?	❑ Very difficult	❑ Difficult	❑ Acceptable	❑ Easy	❑ Very easy	
Would you prefer to use this method for single lung ventilation in the future?	❑ Yes	❑ No	If **no**, please specify:			