Protocol Title:

Evaluation of a disposable flexible bronchoscope, a randomized, controlled, cross-over trial

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Medical Device: Ambu aScope 3
Ambu, Glen Burnie, MD

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1.0 Introduction

1.1 Study Conduct

This study will be conducted in compliance with the protocol approved by the University of Louisville Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the U of L IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such a case, the deviation will be reported to the IRB according to its policies and procedures.

1.2 Background

Flexible bronchoscopy is a frequently performed procedure in the critical care unit(Lucena et al., 2012) as well as in an outpatient setting. The procedure is used for diagnostic and therapeutic purposes in the diseased lung (Rand et al., 2013). One of the main indications for flexible bronchoscopy in the critical care unit is the diagnosis of pulmonary infections in the presence of pulmonary infiltrates and or worsening pulmonary gas exchange. Flexible bronchoscopy allows to conduct a broncho-alveolar lavage (BAL) to both collect specimen for culture, for evidence of alveolar inflammation (Perkins, Chatterjie, McAuley, Gao, & Thickett, 2006) and to clean the patient's bronchial tree from mucus and secretions. (Kreider & Lipson, 2003) The latter represents the therapeutic part of the procedure. By freeing the bronchi from obstructing secretions better aeration will ensue with subsequent resolution of atelectasis and improvement of alveolar gas exchange. (Haenel, Moore, Moore, & Read, 1992; Tsao, Tsai, Lan, Shieh, & Lee, 1990) Less frequent indications for flexible bronchoscopy in the critical care setting are pulmonary hemorrhage, difficult airway management and percutaneous tracheostomy. (Estella, 2012)
Flexible bronchoscopy is an effective and a safe diagnostic and therapeutic procedure in the critical care setting. (Bellomo, Tai, & Parkin, 1992). It is typically well tolerated by

the patient with respiratory compromise including patients with adult respiratory distress syndrome. (Steinberg et al., 1993) In a recent prospective multicenter study more than 20,986 bronchoscopies were included to evaluate the incidence of complication. The study showed that bronchoscopy is associated with a very low incidence of mortality (0.02%) and complications (1%). (Facciolongo et al., 2009)

Since the first flexible bronchoscope was introduced by Ikeda in 1968(Ikeda, Yanai, & Ishikawa, 1968), the technology has been improved steadily. Development of a better image clarity and ease of use has made flexible bronchoscopy a widespread tool in the critical care environment.

Flexible bronchoscopes are typically reusable and therefore need high-level disinfection to prevent inadvertent spread of microbial pathogens from patient to patient. The process of disinfection is time consuming and expensive. Moreover, a bronchoscope being processed may not be readily available for another patient. One solution to this problem was to use a single-use disposable sheath that covers a flexible bronchoscope protecting all surfaces of the bronchoscope. (Colt, Beamis, Harrell, & Mathur, 2000). Another way to eliminate potential hazards with a reusable bronchoscope is the use of a disposable bronchoscope. Such a disposable bronchoscope has been developed (Ambu aScope, Ambu, Glen Burnie, MD) and has been used successfully for intubations in manikins (Scutt et al., 2011) and patients. (Kristensen & Fredensborg, 2013; Pujol, López, & Valero, 2010; Tvede, Kristensen, & Nyhus-Andreasen, 2012). Further advancement in the imaging and handling of this disposable flexible bronchoscope now allows for the purpose of bronchoscopy and broncho-alveolar lavage in critically ill patients with pulmonary compromise. (**FDA approval: 05-11-2013 date**)

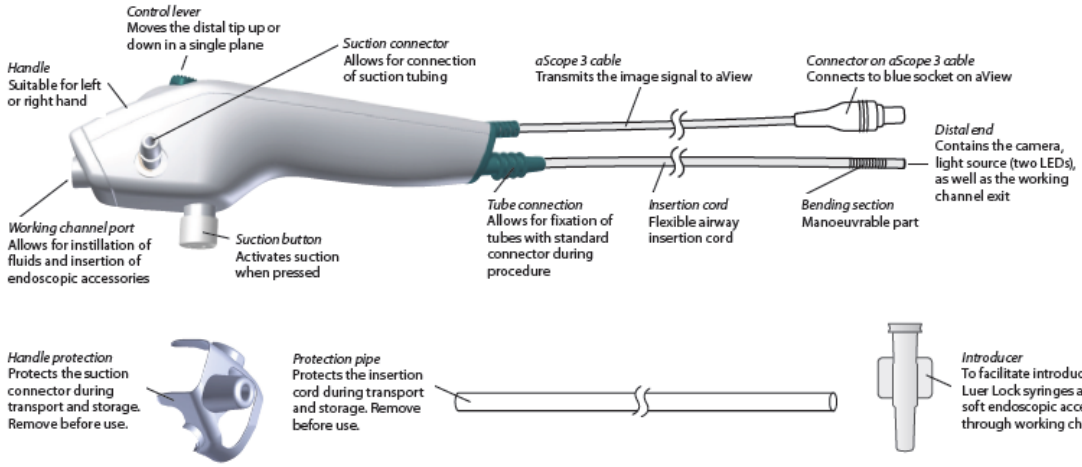
The aim of the study is to compare image clarity, suction capacity, and handling performance of a reusable flexible bronchoscope to the disposable flexible bronchoscope. In addition, we intend to perform a cost analysis.

1.3 Medical Device

1.3.1 Name of Study Device: aScope3

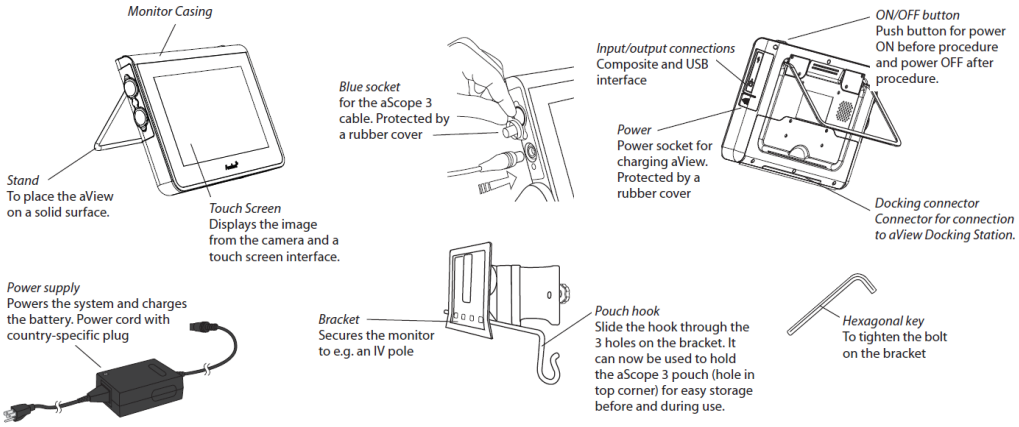
Technical product specifications
The device has 2 main components, the scope and the monitor (aView). Sections below are a schematic representation of the scope and the aView monitor.

aScope 3



aView

The aView displays the video image from the aScope 3. During start up, aView powers up and configures the aScope 3. If the aView battery icon on the screen changes from fully charged to low battery (red battery) within 30 minutes, aView must be replaced.



5. Technical Product Specifications

5.1. aScope 3 Specifications

	aScope 3 Slim	aScope 3
Optical System		
Field of View	85°	85°
Depth of Field	8-19 mm	8-19 mm
Illumination method	LED	LED
Insertion portion		
Bending section[3]	130° up, 130° down°	150° up, 130° down°
Insertion cord diameter	3.8 mm (0.15")	5.0 mm (0.20")
Distal end diameter	4.2 mm (0.16")	5.4 mm (0.20")
Maximum diameter of insertion portion	4.3 mm (0.17")	5.5 mm (0.21")
Minimum endotracheal tube size (inner diameter)	5.0 mm	6.0 mm
Minimum double lumen tube size (inner diameter)	37 Fr	41 Fr
Working length	600 mm (23.6")	600 mm (23.6")
Channel		
Average inner diameter	1.2 mm (0.047")	2.2 mm (0.087")
Minimum instrument channel width[4]	1.2 mm (0.047")	2.0 mm (0.079")
Suction connector		
Connecting tube inner diameter	Ø7mm +/- 1mm	Ø7mm +/- 1mm

5.2. aView Specifications

Display	
Max. resolution	800 * 480
Orientation	Landscape
Display type	8.5" colour TFT LCD
Brightness control	Yes, ("+" / "-")
Contrast control	Yes, ("+" / "-")
Start up time	About 1 second
Memory	
Storage capacity	8GB
Electrical power	
Power requirement	18V 1,67A DC input
Battery type	11,1V 3760mAh

Intended Use of the Investigational Device

1.2. Intended use

The aScope 3 endoscopes have been designed to be used with the aView monitor, endotherapy accessories and other ancillary equipment for endoscopy within the airways and tracheobronchial tree.

1.3.2 The Device is based on a new technology that features single-use bronchoscopy.

2.0 Study Objectives

Our goal is to determine whether aScope 3 (Ambu, Glen Burnie, MD) delivers an adequate image, suction quality, and has a comparable handling performance compared with a standard re-usable bronchoscope (Storz 8402 2x, El Segundo, CA) in the critical-care setting.

3.0 Study Design

3.1 General Design

We propose a prospective, randomized, controlled, crossover study with the plan to enroll 40 subjects in the critical care unit who have the need for a diagnostic and or therapeutic bronchoscopy.

3.2 Study Endpoints

Test the hypothesis that there is no significant difference in performance between the single-use, disposable bronchoscope and the non-disposable bronchoscope. The primary endpoints will be visualization and handling of the two bronchoscopes. Secondary endpoints will be measured suction time and the quality of BAL samples.

4.0 Subject Selection and Withdrawal

4.1 General Characteristics of the Proposed Subject Population

Adult patients 18 and older who are intubated and have an indication for diagnostic and or therapeutic bronchoscopy will be enrolled into the study after patient or patient's legal representative will accept and sign U of L IRB approved Inform Consent Form. We will accept patients from all minority groups. Based on the population of greater Louisville, we expect that 85% of the subjects will be Caucasian. We will include male and female patients in the study.

4.2 Inclusion Criteria

1) Adult 18 years old and older
2) Capable of giving informed consent or have an acceptable surrogate capable of giving legally authorized consent on the subject's behalf.
3) Indication of a diagnostic and or therapeutic bronchoscopy as determined by the attending critical care physician
4) Being cared for in the critical care units at the U of L Hospital

4.3 Exclusion Criteria

1) Patient is moribund and a bronchoscopy is very unlikely to reduce impending mortality or can avert death

4.4 Subject Recruitment and Screening

Subjects will be recruited in critical care Units of the University of Louisville Hospital. The potential complications will be explained to the patient or his/her legal representative twice. First, the patient will have the information presented to them as part of the conventional care consents during their stay in the critical care unit. Second, the patient will have the information presented again when the investigators have a consenting discussion with the potential subjects about the research protocol.

4.5 Early Withdrawal of Subjects

4.5.1 Criteria for Removal from Study
Subject or his/her legal representative consent withdrawal will be a reason for early removal from the study.

4.5.2 Follow-up for Withdrawn Subjects
There is no follow-up in the study.

5.0 Procedures

5.1 Subject management

Patients will be monitored by standard NIBP or invasive arterial lines, ECG and oxygen saturation. All patients are intubated due to their respiratory insufficiency or for airway protection. Patients will be anesthetized for the procedure in the ICU. Anesthesia will be induced with versed 2mg, fentanyl 100 µg and paralyzed with 0.1mg/kg vecuronium. Anesthesia will be maintained with propofol infusion 50-150 µg/kg/min.

All patients will be under general anesthesia as is routine for this clinical procedure. Standard monitoring will be applied. This includes a blood pressure cuff or an arterial line, EKG and a pulse-oximeter. Patients will receive 2 mg/kg propofol, 1µg/kg fentanyl and 0.1mg/kg vecuronium for the procedure. After induction of anesthesia the FiO_2 will be turned to 1.0 and a bronchoscopy adaptor will be interposed in the breathing circuit next to the endotracheal tube.

5.2 Bronchoscopy

Patients will be randomized to receiving either the non-disposable bronchoscope (Storz 8402 2x, El Segundo, CA) or the single use aScope 3 first. After randomization, bronchoscopy will be started with an inspection of the trachea and carina. Next the right lung bronchial tree will be inspected systematically beginning with the right upper lobe,

following with the right middle lobe and finishing with the right lower lobe. All segmental bronchi will be inspected and cleaned by suction as deemed necessary. The bronchoscope will then be removed from the bronchial tree and rinsed with saline Subsequently, the bronchoscope will be re-inserted and advanced to the basal segmental bronchi of the right lower lobe. The tip of the bronchoscope will be brought into wedge position in one of the basal segments for broncho-alveolar lavage (BAL). A saline flush of 20 ml will be administered. The flow of saline will be observed at the distal tip of the bronchoscope. After 10 seconds of maintaining a wedge position, gentle suction will be applied to collect the lavage specimen in the collection trap. This step will be repeated 4 more times (total of 80ml) to obtain an adequate specimen. The same procedure will be repeated on the left lung using the alternate bronchoscope according to randomization. At the end of the procedure, a chest radiograph will be obtained to rule out pneumothorax.

5.3 Measurements

Before starting the procedure the set up time of each bronchoscope will be recorded. The view, image, and light of each bronchoscope will be assessed, then the inspection of the upper lobe segmental bronchi will be conducted. The time of lavage and suctioning until no more specimen can be collected will be measured. The volume of the obtained specimen will be measured. The specimen will be evaluated by a blinded observer after the procedure is completed. (clear fluids, mucous secretions, viscous secretions, pus, blood etc). The blinded observer will evaluate the quality and quantity of the sample for obtaining cultures. The blinded observer will be an attending or resident from the anesthesiology or infectious diseases department.

The overall ease of handling will be rated directly after the procedure by the investigator. All bronchoscopies will be taped and view-clarity, image and light-brightness will be assessed by a second blinded observer. This blinded observer can be another investigator not present during the procedure or an internist who was not present and is part of the study team.

All assessments will be performed using a qualitative scale as 1excellent, 2 good, 3 fair or 4 poor and 5 cannot be evaluated.

6.0 Statistical Plan

6.1 Sample Size Determination

We are planning to enroll 40 patients.

6.2 Statistical Analysis

All measured times will be compared using paired T-tests. Categorical data will be compared using McNemar's test. All data will be expressed as mean ± SD.

Any deviations from the previously described statistical plan will be described and justified in a protocol amendment and/or in the final report submitted to the IDE application.

6.3 Interim Analysis

There is no interim analysis planned.

7.0 Risk Analysis

Bronchoscopy is a well-tolerated procedure. The reported mortality rate is around 0.02% (Facciolongo et al., 2009) Adverse events may be transient fever (5%) and chills(Sharif-Kashani et al., 2010) associated with a non-infective acute inflammatory response with absence of bacteremia (Georgiades et al., 2003; Huang, Bassett, Levin, Montilla, & Ghio, 2006; Um et al., 2004), and bronchospasm (<1%). Bronchoscopy involves several, although rare, risks including mucosal bleeding, development of a pneumothorax with the need of insertion of a chest tube. Another risk may be contamination and (cross)-infection secondary to the insertion of the bronchoscope. In addition, during bronchoscopy there may be a transient decrease in baseline PaO_2 and oxygen saturation may drop to a level below 90%. In this case, bronchoscopy will be interrupted to allow the patient's lungs to recover. Occasionally, the procedure may have to be aborted. At the end of the procedure, a chest radiograph will be obtained to rule out pneumothorax. The only difference to routine bronchoscopy is that we will use two different bronchoscopes, one on each side of the lung, as compared to one non-disposable bronchoscope during routine bronchoscopy.

The proposed study will be conducted with approval of the Human Studies Committees at the University of Louisville. The investigators must receive written, informed consent from participating patients or authorized representatives. The principal investigator and all collaborators have completed an IRB-certified human subject protection-training course.

We will only enroll patients who were admitted to a critical care unit at the University of Louisville and who are intubated.

7.1 Anticipated Risks

The potential complications will be explained to the patient or his/her legal representative twice. First, the patient will have the information presented to them as part of the conventional care consents during their stay in the critical care unit. Second, the patient will have the information presented again when the investigators have a consenting discussion with the potential subjects about the research protocol and anticipated risks.

Possible risk associated with bronchoscopy may include but is not limited to the following:

- Transient hypotension related to sedation (low blood pressure)
- Bronchospasm (spasm of the large passageways in the lung)

- Hypoxemia (decrease in oxygen)
- Bleeding
- Pneumothorax (collection of air inside the chest around the lungs which leads to lung collapse)
- Cardiac arrhythmias (irregular heartbeats)

7.2 Adverse Event Definitions

Adverse effect. Any untoward medical occurrence in a clinical study of an study device; regardless of the causal relationship of the problem with the device or, if applicable, other study treatment or diagnostic product(s).

Associated with the study device. There is a reasonable possibility that the adverse effect may have been caused by the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse effect. Any adverse effect that places the subject, in the view of the investigator-sponsor, at immediate risk of death from the effect as it occurred (i.e., does not include an adverse effect that, had it actually occurred in a more severe form, might have caused death).

Serious adverse effect. Any adverse effect that results in any of the following outcomes: death, a life-threatening adverse effect, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

- Hospitalization shall include any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse effect; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

Unexpected adverse effect. Any adverse effect, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol(s).

Unanticipated adverse device effect. Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol, or any other unanticipated serious problem associated with a study device that relates to the rights, safety, or welfare of subjects.

7.3 Recording of Adverse Events

All observed or volunteered adverse effects (serious or non-serious) findings, or suspected causal relationship to the study device will be recorded in the subjects' case histories. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e. , whether the effect should be classified as serious adverse effect) and; 2) an assessment of the casual relationship between the adverse effect and the study protocol.

Adverse effects felt to be associated with the study device will be followed until the effect (or its sequelae) resolves or stabilizes at a level acceptable to the investigator.

7.4 Causality and severity assessment

The investigator will promptly review documented adverse effects and abnormal test findings to determine 1) if there is a reasonable possibility that the adverse effect was caused by the study protocol or device; and 2) if the adverse effect meets the criteria for a serious adverse effect.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study device/protocol, the adverse effect will be classified as associated with the use of the study device for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study protocol/device this determination and the rationale for the determination will be documented in the respective subject's case history.

7.5 Reporting of Adverse Effects and Unanticipated Problems

In accordance with applicable policies of the UofL Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or volunteered adverse effect that is determined to be (1) unexpected; (2) related or possibly related to the research; and (3) involves increased or greater risk of harm to participant(s) or others than was previously known or approved by the UofL IRB. Adverse effect reports will be submitted to the UofL IRB in accordance with the UofL IRB policies and procedures.

8.0 Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Consistent with these regulations a signed authorization will be obtained that informs each subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

8.2 Source Documents

Study coordinators and research fellows are responsible for data collection.
Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

8.3 Case Report Forms

Coordinators and PI are responsible for case report forms. PI will review the CRFs for accuracy and completion on an ongoing basis throughout the study.
The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

8.4 Record Retention

It is the investigator's responsibility to retain study essential documents during the investigation and for a period of 2 years after the date on which the investigation is terminated or completed.

Research records and original signed consent forms are to be retained by the principal investigator for at least 6 years if the form includes authorization for use of private health information. The 6-year minimum retention of authorizations complies with the privacy regulation requirements.

8.5 IRB Documentation

Regulatory coordinator is responsible for maintaining IRB Correspondence. All UofL IRB approved documents will be maintained as part of the study.

9.0 Study Monitoring, Auditing and Inspecting

9.1 Study Staff Responsibilities and Training.

CITI Training

The investigators and all staff involved in the study will have completed their required U of L Research training.

Protocol Procedure Training
Study staff delegated to conduct specific study procedures will be trained on these procedures individually or in a group format. A record of this training will be kept on the study-training log.

9.2 Safety Monitoring

The **research coordinator** will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB of all Unanticipated Problems/SAE's.

The **research coordinator** and **Principal Investigator** will confirm that all Adverse effects (AE) are correctly entered into the AE log by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; notify the IRB of all Unanticipated Problems/SAEs and AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

9.3 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Research Quality Assurance Office, UofL IRB, and government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities.

10.0 Ethics

This study will be conducted in compliance with the protocol approved by the University of Louisville Institutional Review Board, the relevant federal regulations, and IRB policies and procedures and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such a case, the deviation will be reported to the IRB according to its policies and procedures.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects/LARs to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of all subjects will be sought using the IRB-approved consent form. Before a subject undergoes any study procedure, an informed consent discussion will be conducted and written informed consent obtained with a consent form signed by the subject or legally acceptable surrogate if applicable. An investigator-designated research professional will obtain written informed consent from subjects.

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