Functionality and Accuracy of the smART System in Real-Life ICU Settings

Principal Investigator:	Z Grunwald, MD
Investigational Device:	smART Feeding Tube System
Sponsor:	ART Healthcare, Ltd.
Study Site:	Thomas Jefferson University
Monitoring	ProMedoss

Change History:

Rev.	Description of change	Date
01	First initiation	15 June. 2016
02	• Typos corrections throughout the document • Corrections in the following sections: - Section 1.2- add feeding tube image and Hub description - Section 1.4- add and removing primary endpoints - Section 6.2- add videotaping, remove feeding stop, change removal of feeding tube and used device explanations, detailed Aspiration of gastric contents recording.	07 Dec, 2016
03	Addition of balloon inflation parameters	25 Jan, 2017
04	• Updates interval time between inflations. • Correction to study conduct statements.	31-Aug-17
05	Removal of methylene blue reference and replacement with pepsin test.	11-Sep-17
06	Section 6.2.12.- redefining when patient will be considered officially enrolled in the study	23-Apr-2018
07	Section 6.2.12.- back to protocol rev.05- redefining when patient will be considered officially enrolled in the study (enrollment at consent)	26-June-2018
08	The following paragraphs have been changed: Synopsis, 4.2 and 6.2.3	05-Dec-2018

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List of Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase (also known as glutamate-pyruvate transaminase-SGPT)
AST	Aspartate Aminotransferase (also known as glutamate-oxaloacetate transaminase-SGOT)
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval
Cm	Centimeter
CPK	Creatine phosphokinase
CRC	Clinical Research Center
CRF	Case Record Form
CV	Curriculum Vitae
EC	Ethic Committee
ENT	Ear Nose and Throat
FDA	Food and Drug Administration
GI	Gastrointestinal
hrs	hours
HR	Heart Rate
ID	Identification
min	minutes
mm	millimeters
NPV	Negative Predictive Value
PPV	Positive Predictive Value
psi	Pounds per Square Inch pressure unit
PT/INR	Prothrombin Time/International Normalized Ratio
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
TASMC	Tel Aviv Sourasky Medical Center
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

Synopsis

Study Title:	Functionality and Accuracy of the smART System in Real-Life ICU Settings
Purpose:	To validate the functionality and accuracy of the smART System in areal-life ICU setting
Study Design:	Open, prospective, single arm study
Study Objectives:	1. To verify that the system is able to automatically detect correct placement and tube movement during on-going use 2. To record and analyze impedance levels and reflux episodes 3. To verify that the system stops feeding when the tube is misplaced or reflux is detected 4. To obtain feedback from clinical staff regarding device use and usability 5. To Collect data regarding the occurrence of reflux episodes in relation to patient positioning 6. To quantify the amount of discarded nutritional supplement 7. To demonstrate the safety of the smART system 8. To evaluate the effectiveness of the System to reduce aspiration of gastric contents.
No. of Subjects:	20 subjects
Population:	- ICU ventilated patients - Patients who are receiving PPI therapy during the study - Patients receiving a standard enteral feeding formula - Patients who are hemodynamically and respiratory stable
Investigational Sites:	Thomas Jefferson University
Principal Investigator:	Z Grunwald, MD
Study Duration:	56 hrs. -7 days per patient.

	Overall duration of study is estimated to be 3 months (depending on enrollment rate).
Endpoints:	Primary: Functionality - the system is able to accurately guide the user to ensure correct initial placement (verified by X-ray). - the system is able to detect tube movement/displacement during ongoing use (verified by markings on the tube). - the system automatically stops feeding when tube displacement is detected. - the system automatically stops feeding when reflux is detected. - the system automatically inflates the balloon when a reflux episode is detected Safety - occurrence of device related adverse events Secondary: - Ease of use of the system and the user interface by subjective questionnaire of staff. - Recording of impedance detected by the system and correlation to patient positioning. - Quantification of the amount of discarded nutritional supplement by implementing GRV test as needed and according to hospital procedures. - Reduction of aspiration of gastric contents percentage compared to standard feeding (as reported in literature). - Correlation between patient clinical information and the occurrence of reflux and sensors data.
Inclusion Criteria:	1. Males and females 18 years or older 2. Patient has already been admitted to ICU 3. Patient requires enteral feeding 4. Patients receiving PPI therapy

	5. Informed consent by independent physician and next of kin 6. ICU ventilated patients

1 Identification and Description of the Investigational Device

1.1 Introduction

Supplemental enteral nutrition is commonly used for various indications such as swallowing disorders, inability to ingest food (e.g. head injury, stroke, and anorexia due to an underlying disease) and others. The majority of patients requiring nutritional support will need it for less than one month, and nasogastric tube feeding is by far the most commonly used route of access.

There are a number of potential complications that can occur with naso-enteral tube feeding, the most noted complications are:

Preventing aspiration of gastric content in tube-fed patients

The central cause of **aspiration pneumonia in tube-fed patients is due to aspiration of gastric contents**. There are various tube-fed nursing practices that may help reduce the rate of aspiration, but their efficacy is limited and they are hard to implement. Currently there are no device-based solutions for prevention or monitoring of gastric content aspiration. Aspiration pneumonia (including pneumonitis) has been reported to occur in average of 25-30% of tube fed patients in ICU and ICU 44% to 95% in neuro ICU. In critically ill ventilated patients, enteral nutrition has been shown to be an independent risk factor, increasing the risk for the development of pneumonia by more than five-fold (Drakulovic, et al. 1999). Many researchers believe that in tube-fed critically ill patients it is aspiration of gastric contents that is of greatest concern (Metheny, et al. 2006).

Usually, gastric residual volume tests are routinely performed every 4 hours. These **tests take up valuable nursing resources, are inaccurate, and often lead to unnecessary cessation of feeding**. Gastric emptying of calorie-dense liquid meal is 40%-45% slower in mechanically ventilated patients (Ritz, et al. 2001). Delayed gastric emptying is even more frequent in patients with burns, multiple trauma (with and without head injury) and severe sepsis.
The term "gastrointestinal failure" (GIF) has been used to describe a syndrome of severe gastroparesis. This syndrome is more commonly observed in patients with acute medical and surgical emergencies than in patients undergoing elective surgery and typically develops several days after admission to an ICU. A retrospective study found a 10% incidence of gastrointestinal failure in ICU patients (Mizock 2007).

There exists an urgent need for device and method for the prevention of aspiration pneumonia.

Positioning nasogastric feeding tubes

Insertion of nasal feeding tubes can be performed blindly at bedside or with fluoroscopic or endoscopic guidance into the stomach.

Although generally safe and effective, they are usually inserted blindly at the bedside and there is a **wide spectrum of known complications associated with feeding tube placement**. The most common serious complication is misplacement of the feeding tube into the bronchial tree with resulting pneumonitis, pneumonia, and/or pneumothorax if not recognized. This is reported to occur in **2.4%–3.2% of nasogastric insertions** (James L, et al. 2012).

Recent studies have suggested that 0.1 to 0.3% of all patients who were blindly placed of their feeding tubes die as a result of bronchopulmonary injury from misplaced tubes (Sorokin R et al. 2006) (Aguilar-Nascimento JE, et al. 2007).

It is estimated that **approximately 1.2 million feeding tubes are placed each year in the United States alone** (Koopmann MC et al. 2011). If these tubes were placed blindly this would translate to **3,600 to 8,400 pulmonary injuries, and 1,200 to 3,600 deaths in the United States each year**.

Hundreds of thousands of patients require NG tubes each year in the UK. Although the precise number is not known, the NHS Purchasing and Supply Agency (PASA) which distributes NG tubes has estimated that between 750,000 to 1,000,000 tubes are used each year within the NHS1. In addition to those used within the NHS, private hospitals, hospices and nursing homes are expected to greatly increase the number of tubes used annually. Currently, X-ray is the gold standard method for detecting the position of nasogastric tubes (Hedberg et al, 2005). However, staff does not use it routinely due to cost, risk of radiation exposure, and delay in feeding (National Patient Safety Agency, 2011; 2005). In addition, the National Patient Safety Agency (NPSA) has drawn attention in 2011 to the risk of misinterpretation of X-rays used to confirm the position of a nasogastric tube.

Positioning complications are also occurring throughout the duration of the use of the tube. Movement of the distal tip of the feeding tube occurs even when the NG tube is taped in place. This is most likely to occur with soft, small-bore NG tubes. Malpositioning of the indwelling tube may result in injury or aspiration.

The smART™ Feeding Tube System is a novel feeding tube developed by ART Healthcare Ltd. to overcome feeding tube displacement and reflux prevention and the complications associated with them. The smART Feeding Tube is equipped with sensors designed to provide information about the location of the tube tip relative to the lower esophageal sphincter as well as a balloon intended to aid in the prevention of aspiration due to reflux episodes.

The aim of the clinical study proposed in this protocol is to assess this new device in the clinical setting model.

1.2 Device Description

The smART™ Feeding Tube System (sFTS) is a novel system with feeding tube developed by ART Healthcare Ltd, based on sensor-lined tubes that transmit real-time information to an external console. The smART™ feeding tube is equipped with a balloon which serves as an anti-reflux mechanism to prevent the gastric contents from regurgitating to the upper portion of the esophagus thus reducing the risk for aspiration. In addition, the smART™ feeding tube is equipped with sensors designed to provide information about the location of the tube tip relative to the lower esophageal sphincter (LES) thus assisting in reducing the incident of misplacement during first positioning. The smART™ feeding tube is also connected to a motorized mechanism which automatically and in real-time stops feeding if the feeding tube moves out of position during ongoing use or detect gastric content in esophagus. Furthermore, smART™ Feeding Tube System can guide operator to correctly re-position the tube in case of tube migration while feeding.

To minimize the risk of pressure build-up in the stomach and esophagus as a result of the balloon inflation, the company has added an additional safety feature (figure 2). This feature allows for gastric content to escape through the feeding tube into a collection bag. The concept behind this mechanism is simple, once the console detects a reflux episode it automatically stops feeding via clamping and inflates the balloon. The safety feature triggers a release clamp to open, thus allowing gastric content to climb up the feeding tube and release any pressure that may raise within the patients' stomach upper GI tract.

The smART™ Feeding Tube System contains the following (figures 1, 2 and 3):

a) **Feeding tube** – consisting of the following:

- Multi-lumen, made of medical grade material (figure 1a)
- Y-Shaped Feeding inlet, with standard dimensions, made of medical grade material and compatible with ENfit connectors for feeding set and GRV Drainage bag connections, as shown in figure 1b. The Y – Shaped port also connects to a gastric content bag. This feature was added to overcome risks associated with pressure build-up in the stomach and esophagus due to balloon inflation. Gastric contents will pass through the feeding tube and accumulate in the connected collection a bag (figure 2).
- Impedance sensors, which are made of medical grade SS316 wire. The sensors are located in a number of locations along the feeding tube as well as above the balloon to allow the

system to identify weather it actually prevented the gastric content from climbing up the esophagus.

- Hybrid connector, which has PCB electric contacts and one air conduit – Not in contact with the feeding liquid or the patient body.
- Balloon made of medical grade material.

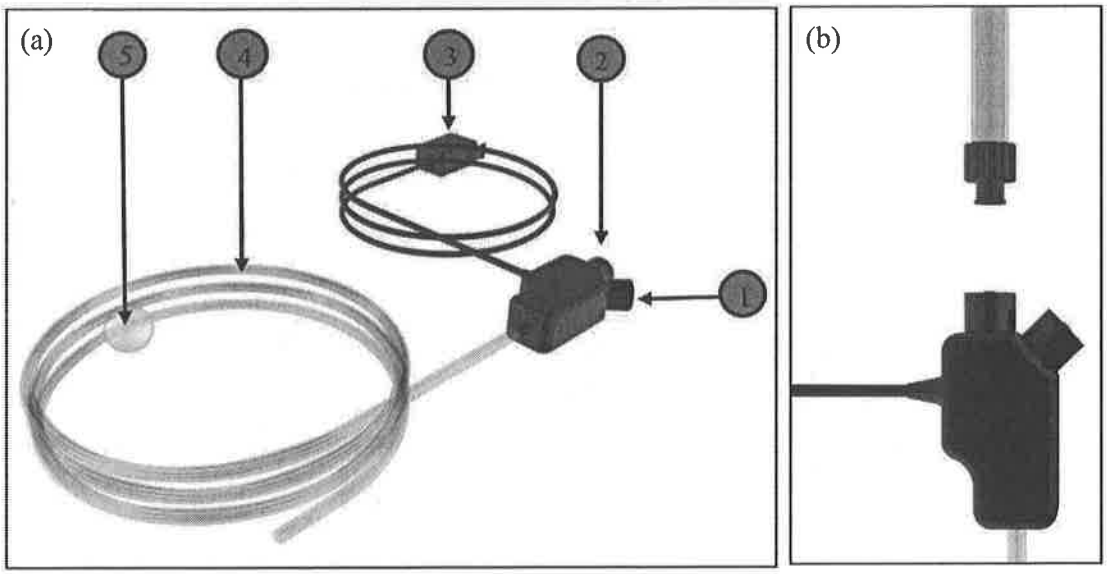

Figure 1: a) smART™ Feeding Tube and feeding connector. b) ENfit connectors for feeding set and GRV Drainage bag connections

1. Y connector- ENFit connection to feeding set
2. Y connector- ENFit connection to GRV Drainage bag
3. smART™ Feeding Tube hybrid connector- feeding tube connection to HUB inlet.
4. smART™ Feeding Tube with Sensors
5. Balloon

b) **Electronic console** (12V power supply operated) which:

- Indicates the location of the tube in the body.
- Inflates and deflates the balloon as needed
- Stops the feeding when feeding tube is out of position during ongoing use.
- Keeps a patient event log The electronic console components include:
- Electronic box, which serves as the interface for the system.

- Stand AC adapter, which allows connecting the electronic console to standard IV stand pole.

c) The Hub:

- The smART™ HUB (Figures 2 and 3) is located at the bedside mounted on a pole. It is connected to the rear panel of the console using a "build in" cable that comes out from the Hub.
- ~~Additional connection between smART™ ENFit feeding inlet of the feeding tube Y connector.~~
- The smART™ Hub has an indicator light that shows the HUB's state

Figure 2: the smART Feeding Tube System

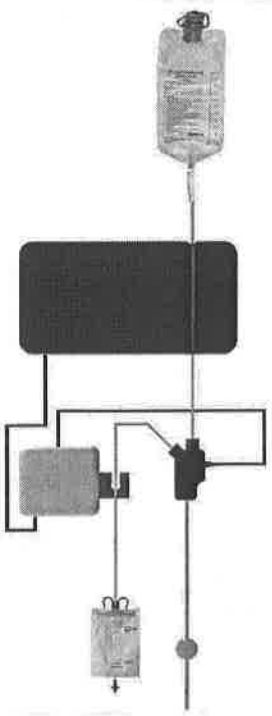

Figure 3: Pressure Build-Up Safety Mechanism

1.3 Intended Use

The smART™ Feeding Tube is intended for gastric decompression, gastric lavage, and the administration of nutrition, fluids and medications for patients who have an intact gastrointestinal tract but are physically unable to manage nutritional intake through normal mastication and deglutition

The smART™ Feeding Tube System serves as an anti-reflux mechanism, by using a balloon, which prevents the gastric contents from regurgitating to the esophagus thus reducing the risk for aspiration of patients requiring enteral feeding. The smART™ System is also designed to aid qualified operators in the placement of the smART™ Feeding Tube into the stomach during initial placement thus assisting in reducing the incidence of misplacement during first positioning. Furthermore, smART™ Feeding Tube monitors the position continuously during the course of the feeding and automatically provides real time alerts of tube migration. smART™ System also can guide the operator to correctly reposition the tube.

1.4 Intended Users and Training Requirements

The smART™ System is indicated for the same patient population as other commercially available feeding tubes, namely, patients in need of enteral feeding and administration of medications. The smART™ feeding tube will be introduced to patients by the medical staff qualified to introduce commercially available feeding tubes. During site initiation, all site staff that have been identified as device operators will receive training by the sponsor in order to ensure correct use of the device throughout the study.

1.5 Manufacturer and Manufacturing Information

The smART™ System was designed and is manufactured by Art Healthcare. Details on the manufacturing of the system are provided in the Investigator's Brochure.

1.6 Device Procedure

The use of the smART™ System is substantially similar to the use of commercially available feeding tubes. The smART™ System includes the added feature of facilitating correct tube placement and alerting when tube is displaced during ongoing use. The system will automatically stop feeding if displacement is detected. If a reflux episode is detected by the system, a balloon located on the tube will automatically inflate to prevent gastric content from regurgitating to the esophagus. The balloon inflation parameters are as follows:

- Maximum balloon pressure: 30 mmHg
- Maximum inflation duration: 5 minutes
- Minimum duration between balloon inflations: as long as the previous inflation period

2 Risks and Benefits

The smART™ System is designed according to international standards for medical devices. Compliance with these standards ensures that the device can be used safely in humans.

Biocompatible materials are used for the feeding tube components. The use of biocompatible materials should protect the patient against possible biomaterial related adverse events.

ART Healthcare follows and complies with the risk management standard ISO 14971:2012 and ISO 14971:2007. Extensive design verification & validation bench and animal tests were performed to mitigate all risks detected, in accordance with essential requirements listed in the Medical Device Directive (MDD 93/42/EEC).

In addition, a feasibility study on 10 healthy volunteers was completed with the (smART™ System).

The results of the study supported the company's claim that the insertion, balloon inflation and feeding with the smART™ feeding tube are safe and tolerable. The results also show that the device aids in the correct placement of the feeding tube into the patient.

2.1 Anticipated Clinical Benefits

The purpose of this study is to evaluate the ability of the system to aid in the correct initial placement of the feeding tube, detect tube malpositioning during ongoing use, as well as prevent gastric content from regurgitating to the esophagus. With validation of the above features during the study, the clinical benefit of the device will be the lowering of risks associated with tube displacement and malpositioning as well as lowering the risk associated with reflux and aspiration.

2.2 Anticipated Adverse Device Effects

Mild discomfort in the throat is anticipated with the insertion of the feeding tube, as with all other feeding tubes which are used in clinical situations. Minor internal skin irritation may occur due to balloon inflation.

2.3 Residual Risks Associated with the Investigational Device

No residual risk is anticipated with the investigational device.

3 Study Objectives

The primary objectives of this study are:

1. To verify that the system is able to automatically detect correct placement and tube movement during on-going use
2. To record and analyze impedance levels and reflux episodes
3. To verify that the system stops feeding when the tube is misplaced or reflux is detected
4. To obtain feedback from clinical staff regarding device use and usability
5. To Collect data regarding the occurrence of reflux episodes in relation to patient positioning
6. To quantify the amount of discarded nutritional supplement
7. To evaluate the effectiveness of the system to reduce aspiration of gastric contents.

4 Study Endpoints

4.1 Primary Endpoints

Functionality

- the system is able to accurately guide the user to ensure correct initial placement (verified by X-ray)
- the system is able to detect tube movement/displacement during ongoing use (verified by markings on the tube)
- the system automatically stops feeding when tube displacement is detected
- the system automatically stops feeding when reflux is detected
- the system automatically inflates the balloon when a reflux episode is detected

Safety

- occurrence of device related adverse events

4.2 Secondary Endpoints

- Ease of use of the system and the user interface by subjective questionnaire of staff
- Recording of impedance detected by the system and correlation to patient positioning
- Quantification of the amount of discarded nutritional supplement by implementing GRV test as needed and according to hospital procedures
- Reduction of aspiration of gastric contents percentage compared to standard feeding (as reported in literature).
- Correlation between patient clinical information and the occurrence of reflux and sensors data.

5 Study Conduct & Population

This study will be performed in accordance with the design and specific provisions of this protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, that are consistent with Good Clinical Practice (GCP), Title 21 of the Code of Federal Regulations (21 CFR), part 812 (Investigational Device Exemptions), and the applicable regulatory requirements.

5.1 Inclusion Criteria

1. Males and females 18 years or older
2. Patient has already been admitted to ICU
3. Patient requires enteral feeding
4. Patients receiving PPI therapy
5. Informed consent by independent physician and next of kin
6. ICU ventilated patients

5.2 Exclusion Criteria

1. Patients with anomalies or diseases of the esophagus and or stomach.
2. Patients with known sensitivities or allergies to any of the feeding tube materials
3. Inability to place patient in semi-Fowler's position.
4. Any clinically significant abnormality upon physical examination which may, in the opinion of the investigator, pose difficulty in inserting the feeding tube (e.g. cervical spine disorder)
5. Pregnancy
6. Recent abdominal surgery (less than 30 days)

5.3 Duration of Study

Each patient may be enrolled in the study for a duration of 2.3 days (56 hrs.±2) up to 7 days (168 hrs.±2). No follow-up will be conducted for this study. Overall study duration is estimated to be 3 months (depending on enrollment rate).

6 Study Treatment

6.1 Type of Study

This is an open, prospective, single arm study in which the investigational device will be tested in real-life settings on patients admitted to the ICU who require enteral feeding.

6.2 Study Design

Due to the sensitive nature of potential study subjects (e.g., unconscious, critically ill, etc.), independent physician and next of kin must sign informed consent prior to initiating any study related activities.

6.2.1 Screening

All patients already admitted into the ICU who require enteral feeding may be screened for potential enrollment into the study. Patients may be included only if they meet the inclusion/exclusion criteria and informed consent has been obtained by independent physician and next of kin.

History and physical examination will be performed in order to assess subject inclusion eligibility.

For women of childbearing age, a urine (or blood) pregnancy test will be performed.

The following information will be recorded for each patient found eligible to participate in the study:

- Medical history (including concomitant medications)- detailed in the CRF.
- Physical examination

6.2.2 Treatment

Following the screening procedure staff will utilize the smART System to provide enteral feeding to the patient. Feeding tube insertion and commencement of feeding should be done per patients' need and per local hospital procedures.

6.2.3 Study Specific Procedures:

- Videotaping of subject

  Following the completion of the informed consent procedure and prior to feeding tube placement, a video recording of the patient will commence. The camera will be placed across from the patient focusing on the facial area and will allow recording of any movement of the tube for later comparison with the data logs recorded by the smART console. All recorded data must be attached to the CRF and serves as an integral part of the analyzable data for the study.

  Specific video procedures will be supplied to the site as part of the study MOP binder.

- Initial Tube Placement:

  Vital signs should be noted within 10 minutes of feeding tube insertion.

  Study staff should follow the device instructions for use and specific instructions provided by the console during initial tube placement. Time of tube placement is recorded by the console.

Once initial placement is confirmed by the system, verification of correct placement should be performed by abdominal X-ray (gold standard). Note: X-ray should be performed as needed and according to hospital procedures. Once placement confirmation is obtained via x-ray, staff should use a permanent marker to indicate the edge of the nostril on the feeding tube (this mark will enable the staff to verify malpositioning warnings if they occur during on-going use).

- Ongoing Use

  If system alerts of tube displacement during ongoing use, staff should record the event and verify based on the tube marking if malpositioning occurred and document the event. The need for tube reinsertion/repositioning should be evaluated and performed as needed.

  When a reflux episode is detected by the system, the following will be initiated:

  1. feeding stops
  2. feeding tube balloon will automatically be inflated by the system
  3. an alert will sound
  4. The Y-piece block opens allowing for feeding system decompression initiating free flow of gastric content into the collection bag. The system will automatically record data relevant to reflux episodes and store it.

- Feeding Information

  Patient information will be recorded from hospital source at the end of the study for each patient. The information will include feeding times, food amounts and types, medications provided, patient positioning, GRV times and amounts.

- Gastric Residual Volume (GRV)

  Local site procedure for GRV should be followed as needed and according to hospital procedures. Every occurrence of GRV is supposed to be recorded by the medical staff in hospital sources (according to hospital standards).

- Patient Positioning

  Every occurrence of patient re-positioning is supposed to be recorded by the medical staff in hospital sources. This information will later be correlated to the occurrence of reflux as recorded by the system.

- X-Ray imaging

  Local site procedure for X-ray should be followed as needed and according to hospital procedures. Each time a thorax x-ray image is taken (as part of the patient care). Once feeding tube initial positioning is performed, X-Ray should be taken as part of the usual gold-standard care. A copy of the X-ray should be documented as part of the study CRFs/Forms.

- Patient general clinical information

  In addition to the CRF's, patient clinical information will be collected directly from the hospital's electronic medical record by the hospital's IT department and provided to the sponsor. The clinical information may include a summary and daily reports and diagnosis, vital signs, imaging data, medications and laboratory reports, breathing and respiratory support parameters, physicians and nurses' notes and medical orders, etc.

  The collected information will include valid data from 48 hours prior to feeding tube insertion up until 24 hours after the end of the study.

  This information will allow for the analysis of the secondary endpoint dealing with the correlation between patient clinical information and the occurrence of reflux and sensors data.

  The data may be collected at various time intervals during the study or at the end of the study once all patients have completed the study.

- Removal of feeding tube

  Every smART feeding tube removal should be documented in the CRF and the relevant device information (i.e., serial number) should be recorded. If a smART tube is replaced by a different smART tube, the reason for replacement should be documented and the serial number of the new device being used should be recorded.

- Endoscopy/esophageal imaging

  One third of the study population will undergo endoscopy to evaluate potential trauma to the esophagus as a result of balloon inflation.

  Endoscopy will be indicated for those patients who:

  - Have been enrolled in the study for a duration of more than 5 days;

  Or,

  - Had noticeable blood residue on the feeding tube following tube removal.

If by the time patient number 13 is enrolled, no endoscopies have been performed, the remaining 7 patients will undergo endoscopy for local evaluation of trauma in the area of the esophagus where the balloon is inflated.

Every effort will be made to obtain at least 7 patients with endoscopic assessment.

Procedure - Following tube removal (within 5 hrs.) patients eligible for endoscopy (based on the above definition) shall undergo an endoscopic procedure to evaluate the balloon inflation site. Specifically, any noticeable trauma to the esophagus shall be recorded in the relevant CRF pages (e.g., adverse event form).

- Aspiration of gastric contents recording

  Local site procedure for tracheal suction should be followed as needed and according to hospital procedures. Once every eight hours a sample of at least 2 cc should be instilled in a LUKI trap. The sample should be appropriately labeled and recorded by the medical staff in the bed side CRF log (Pepsin Test). The sample should be kept frozen until transportation to the lab.

- Used/Unused Devices

  Used devices will be returned back to the bag in which they were provided in by the sponsor. All the bags will be collected by the sponsor, and accountability logs will be updated accordingly.

  All unused devices and study materials will be collected by the sponsor at the end of the study.

- Staff Questionnaires:

At the end of the study, staff will be required to complete a usability questionnaire assessing the ease of use and functionality of the device (refer to Appendix 2).

6.2.4 Medical History

During the screening process patient demographic and medical information acquired from the patient or the patient's medical chart, including previous medical history, medications, history of clinically significant abnormalities of all body systems; concurrent diseases; relevant past medical history.

The relevant information will be recorded in the case report forms for all patients participating in this study.

6.2.5 Physical Examination

During the screening process all patients will undergo a physical examination by an authorized physician. The physical examination will include diagnosis and documentation of any significant abnormalities or diseases relevant to the placement and utilization of the feeding tube.

6.2.6 Study Schedule

Procedures	Screening/ enrollment	Medical Device Placement	Ongoing use	Termination
Day	1	1	Up to 7	2.3 up to 7
Informed Consent	+			
Eligibility Criteria	+			
Physical Exam	+			
Pregnancy test (if applicable)	+			
Vital Signs		+	+	+
Lab Data				+
Medical Device Administration		+	+	
GRV Measurements			+ as needed and according to procedures	
Aspiration of gastric contents recording			+	
Pepsin Test			+ Collected every 8 hrs. during routine tracheal suction	
Adverse Events	+	+	+	+
Concomitant Medication		+	+	+
Patient positioning		+	+	

Information regarding nutritional supplement administration		+	+	
Patient responses		+	+	
Endoscopy (performed on up to 7 subjects)			+ if blood residue is visible on balloon following tube removal (within 5hrs. of tube removal)	+ On subjects enrolled for a duration of more than 5 days (within 5hrs. of tube removal)

6.2.7 Study End

Study participation for each patient will end in the following cases:

- Subject has reached the maximum 7-day duration of participation
- Subject is being transferred to a different ward/facility
- Patient withdrew consent
- Related adverse event
- Death

6.2.8 Deviations from study protocol

Any deviations from the study protocol should be reported to the sponsor and documented on study deviation forms.

6.2.9 Investigative Center Selection Criteria

The investigative site will meet the following selection criteria prior to inclusion in this study:

- Clinical research study experience and resources that demonstrate good compliance with study requirements and timely, complete documentation of subject data.
- Sufficient subject volume to meet enrollment timeframe.

6.2.10 Replacement of Feeding bag

During the procedure, feeding bag should be replaced as needed.

6.2.11 Tracheal suction

During the study, tracheal suctioning will be performed in accordance with hospital procedures. Once every eight hours a sample of tracheal suction of at least 2 cc, will be instilled in a LUKI trap and stored in a freezer to later be shipped to a lab for analysis.

6.2.12 Replacement of Subjects

All subjects that participate in the study for a duration of 2.3 days (56 hrs.±2) up to 7 days (168 hrs. ±2), at termination will be considered as complete. In case of premature withdrawal of subjects from the study (i.e., withdrew prior to participation of 56 hrs.±2), additional subjects may be enrolled to reach the target number following a discussion between the Principal Investigator and the Sponsor. New subjects will undergo the same procedures and assessments as specified in the protocol.

A patient will be considered officially enrolled in the study once signing ICF obtained.

6.2.13 Subject Identification and Confidentiality

A subject's case number will be composed of a two-digit number that represents the sequential serial number of study enrollment at the site and initials.

All reports and communications relating to study subjects will identify the subject only by his case number, initials and unique identification code. The subject identification will be kept confidential at the investigational site according to the local SOPs.

6.2.14 Subject Withdrawal or Discontinuation

Each subject (or delegate) will be informed of his/her right to withdraw from the study at any time and for any reason.

The Investigator may withdraw a subject from the study at any time if he considers that remaining in the study compromises the subject's health.

Additional criteria for withdrawal:

- The insertion of the feeding tube has failed after **2** attempts in each nostril

The reasons for any subject withdrawal will be recorded on the study completion form of the CRF. The investigator will inform the Sponsor in writing of the subject's early withdrawal for any reason.

If withdrawal is caused by an adverse event that the investigator considers may be related to the device, it will be reported to the IRB and to the Sponsor.

6.2.15 Replacement of Feeding tube

During the feeding, feeding tube replacement is allowed in the following cases:

- Feeding tube blockage
- Visual related
- Alarm or warning related to feeding tube according to the user manual.
- The medical staff decision to stop feeding and remove the feeding tube due to unrelated medical reasons.
- Other medical reasons unrelated to feeding process.
- Routine procedures

In the above cases, after replacing the feeding tube with a new one, the patient will continue the study to the remaining time of the study duration. Visual inspection of feeding tube should be performed as indicated in section 6.2.3 Study Specific Procedures.

7 Adverse Events, Adverse Device Effects and Device Deficiencies

7.1 Definitions of Adverse Device Effects and Adverse Events

7.1.1 Adverse Device Effect (ADE)

An "Adverse Device Effect" is an adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event 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.

NOTE 2- This includes any event that is a result of a use error or intentional misuse.

"Adverse Events" are defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons 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 involved (any procedure in the clinical investigation plan).

NOTE 3: For users or other persons this is restricted to events related to the investigational medical device.

All adverse events will be graded for severity as follows:

Mild: Sign or symptom, usually transient, requiring no special treatment and generally not interfering with usual activities.

Moderate: Sign or symptom, which may be ameliorated by simple therapeutic measures; yet, may interfere with usual activity.

Severe: Sign or symptom that are intense or debilitating and that interfere with usual activities. Recovery is usually aided by therapeutic measures.

The relationship of the adverse event to the treatments or procedures is defined as follows:

Probably related: Follows a reasonable temporal sequence from study device delivery/retrieval, and cannot be reasonably explained by known characteristics of the subject's clinical data or the surgical procedure applied.

Possible related: Follows a reasonable temporal sequence from study device delivery/retrieval but could have been produced by the subject's clinical state or by the surgical procedures regardless of the study device.

Not related: No relationship to study device activation is perceived.

7.1.2 Anticipated Adverse Events

Anticipated adverse events associated with the insertion and presence of feeding tubes include:

- Inconvenient sensation in the neck or chest during or after insertion of the feeding tube and during feeding.
- Nasal bleeding during insertion attempt of the tube.
- Difficulty in breathing, coughing and chest pain due to insertion of the tube, mistakenly, into the trachea.
- Difficulty in swallowing due to the presence of the tube.
- Nausea and vomiting

Anticipated adverse events associated with feeding are:

- Abdominal discomfort and pain
- Abdominal bloating
- Diarrhea

7.2 Definitions of Serious Adverse Device Effect and Serious Adverse Event

7.2.1 Serious Adverse Device Effect (SADE)

A "Serious Adverse Device Effect" is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

7.2.2 Serious Adverse Event (SAE)

A "serious Adverse Event is an 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 device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. 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.

7.2.3 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report

7.3 Adverse Event Reporting

All adverse events will be recorded on the adverse events page of the CRF.

Severity and relationship to study device will be assigned by the investigator as described in the section above.

Adverse events will be recorded after the subject (or delegate) has signed the informed consent and throughout the study including the follow-up termination visit. Adverse events should be reviewed and updated at each subsequent visit and during any phone contact with the subject.

Any SAE, whether deemed device-related or not, must be reported to the site Ethics Committee and to the sponsor's Safety Medical Officer by telephone and by Fax, as soon as possible after the investigator has become aware of its occurrence even if not all the information is available at the time of initial contact:

Safety Medical Officer contact information:

Dr. David Gratch

Phone: 215-955-6161

Email: david.gratch@jefferson.edu

The investigator must complete a SAE Form, and send it, via fax, to the Sponsor within 24 hours of becoming aware of the event. Accompanying documentation, such as copies of hospital case reports, autopsy report, and other documents when applicable, should be sent as soon as they are available.

The site's Ethics Committee must also be duly notified and dealt with, according to the local and federal regulations.

Subjects who have had an SAE must be followed clinically until all parameters (including laboratory) either have returned to normal or are stabilized.

8 Monitoring Plan

Monitoring functions shall be performed in compliance with Good Clinical Practices, EN ISO 14155:2011, as outlined in 21CFR§821.43(d) and 21CFR§812.46, and according to any other local regulations.

ART Healthcare will appoint a Clinical Monitor for this study. The Clinical Monitor should be qualified by training and experience to oversee the conduct of the study. The Clinical Monitor's responsibilities include maintaining regular contact with the investigational site, through telephone contact and on-site visits, to ensure that: 1) the study protocol is followed; 2) that complete, timely, and accurate data are gathered; 3) that problems with inconsistent and incomplete data are addressed; and 4) that complications and Unanticipated Adverse Device Effects are reported to the Sponsor.

9 Statistical considerations

9.1 Sample Size

The purpose of this study is to validate the functionality and accuracy of the smART System in real-life ICU settings by field study design. Therefore, descriptive statistics will be used to evaluate

the results. The proposed sample size of 20 subjects is sufficient to assess the performance of the smART™ Feeding Tube for the criteria presented in the primary endpoint. It should be noted that this figure does not include margin of dropout cases (not related to the device) which is normally estimated to be up to 10%.

9.2 Statistical Analysis

The analyses will be carried out according to intention to treat as well as per protocol. Categorical parameters will be summarized by frequencies and percentage, while quantitative variables will be summarized by mean, median, standard deviation and range. In particular, the following tests according to the parameter type will be performed:

- Continuous parameters will be presented by the estimated value and calculation of 95% confidence intervals.
- Nominal categorical parameters will be analyzed by Fisher exact test/ chi-square tests (in case of low observed frequencies).
- Ordinal categorical parameters will be analyzed by Wilcoxon rank sum test.

Alternatively, if data will support the assumption of normality:

- Comparison between continuous parameters will be analyzed by the appropriate Student T-test.

10 Data Management

Data from each subject will be recorded by the hospital (as needed and according to hospital procedures) and will transmitted manually to CRFs supplied by the sponsor. Quality check for errors and omissions will be performed to ensure the accuracy of the entered data. Information to be transmitted from the hospital source to the company CRF includes (but is not limited to): patient position changes, patient feedings, GRV (gastric residual volume), vital signs and medication record, etc.

The source data should be completed during the study by qualified personnel. All data must be filled out using ball pens (not pencils), accurately and promptly following each relevant step of the study. The CRF should be completed in full, i.e., no fields should be left blank once the subject has completed the study. CRFs entries corrections must be made only by lining out (single line) incorrect data and writing in the revisions. All corrections must be initialed and dated by the individual performing/recording the correction on the day of correction. If the reason for the change is not obvious, an explanation for the change should be recorded and attached to the CRF. Blacking out or using correction fluid or an eraser is not allowed to correct or eliminate data. The investigator

must review the CRFs for completeness and accuracy and must sign/date the forms where indicated. Signature stamps or substitutes are not acceptable.

The investigator will retain originals of CRFs, subject consent forms, and study data as permanent records for a period of 2 years or until the data is no longer required for regulatory purposes (the longest between these two).

Each set of CRFs should be reviewed by the sponsor's appointed monitor for accuracy and completion (signatures, dates, adverse events, serious adverse events, protocol deviations).

Using the software auxiliary tables, the following steps will be performed to protect patient privacy and to identify the user who collects the data:

- Define user and password for each nurse that will be authorized access nurse form tab.
- When exporting the CRF table to PDF (for signing purpose), each user that filled the data will have to sign.
- The system properties tab will be password protected and will be access only by ART-Healthcare's staff.

11 Amendments to the Protocol

No alterations or changes to this protocol will be permitted. However, should there be question or consideration of deviation from the protocol, clarification and approval must be sought from the sponsor.

Protocol modifications must be confirmed in writing prior to implementation.

12 Deviations from Study Plan

All major protocol amendments must be approved by the local IRB prior to implementation.

No protocol amendments should be adopted without prior written approval from the IRB except in the following cases:

- In order to eliminate immediate hazard to the subjects
- Changes involving only logistical or administrative aspects of the trial.

The investigator should document and explain any deviation from the approved protocol and to file waivers received from the sponsor, if applicable. Justification, and, if appropriate, the proposed protocol amendments should be submitted to:

1. The Sponsor for agreement
2. The IRB

Any subject treated in a manner that deviates from the protocol, or who is admitted into the study but is not eligible according to the protocol, may be ineligible for analysis and thereby compromises the study.

13 Device Accountability

ART Healthcare will provide the study site with the smART Systems for the duration of the study. The systems will be marked "for investigational use" and the investigator is responsible for storing the systems in a secure place to avoid unauthorized use.

Immediately upon completion of the study all systems and unused tubes will be return to ART Healthcare.

14 Statements of Compliance

This study will be conducted in compliance with the protocol after approval of the local Institutional Review Board (IRB) Committee, in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with Good Clinical Practice (GCP) for medical devices per ISO 14155:2011, title 21 of the Code of Federal Regulations (21 CFR), part 812 (Investigational Device Exemptions), and the applicable regulatory requirements.

No deviation from the protocol, after sponsor's and Ethic Committee approval will be implemented without the prior review and approval except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Ethic Committee and the sponsor as soon as possible.

A copy of the protocol, Informed Consent Form (ICF) and advertising material must be submitted to the IRB. Written approval of the protocol, the Informed Consent Form and advertising material must be obtained prior to initiation of the study.

15 Informed Consent Process

Due to the sensitive nature of potential study subjects (e.g., unconscious, critically ill, etc.), independent physician and next of kin must sign informed consent prior to initiating any study related activities.

The Principal Investigator or his designee in accordance with institutional policy will obtain an Informed Consent, acceptable by the institution's IRB Committee. A written consent form bearing the full name of the subject and the signatures of the subject's delegate and an independent

physician will be obtained for each subject. The signed Informed Consent constitutes a confidential document and therefore should be archived in the Investigator File or in the Site's Record

The written Informed Consent form and any other written information to be provided to subject/delegate should be revised if any important new information becomes available that may be relevant to the subject's consent. Any revised written Informed Consent form, and written information must be approved by the IRB Committee before it is made available for re-signing. The subject's delegate should be informed in a timely manner if new information becomes available that may be relevant to the willingness of the delegate to keep the subject in the study. The communication of this information should be documented.

Neither the investigator, nor the trial staff, should coerce or unduly influence a subject/delegate to participate or to continue to participate in a trial.

The investigator, or a person designated by the investigator, should fully inform the subject/delegate of all pertinent aspects of the study including the approved written informed consent.

Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject/delegate ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject.

Prior to a subject's enrollment into the study, the approved informed consent form should be signed and dated by the delegate, by an independent physician and by the person who is authorized to conduct the informed consent discussion.

16 Vulnerable Population

Most of the participants in this study will likely fall under the definition of "vulnerable population" (e.g., critically ill, unconscious, ventilated, etc.). Due to the sensitive nature of the study participants it is important to thoroughly explain the study to a delegate who is legally allowed to make medical decisions for the subject. Ample time should be given to the delegate to weigh and consider participation in the study. Patient/delegate is allowed to withdraw consent any time during the study. Informed consent signed by the patient (after gaining consciousness) may be obtained within reasonable time of up to two weeks from the end of the study (for the current patient).

17 Suspension or Premature Termination of the Study

The Sponsor reserves the right to discontinue the study at any time for any reason based on (but not exclusively) the following criteria:

- Technical problems in the smART device.

- Unexpected adverse effects.
- The Principal Investigator's or the Ethics Committee recommendation
- Poor performance or compliance of the clinical site
- Company considerations

In case of premature termination of the study, the IRB Committee will be duly informed according to the local regulations.

18 Publication Policy

Any presentation/publication of complete/partial study data by the Investigators or any other party is stipulated by written authorization from the sponsor.

19 References

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4. Stayner JL, Bhatnagar A, McGinn AN, Fang JC. Feeding Tube Placement: Errors and Complications. Nutr Clin Pract 2012;27:738-48.
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9. National Patient Safety Agency (2011) Patient Safety Alert 002: Reducing the Harm caused by Misplaced Nasogastric Feeding Tubes in Adults, Children and Infants. London: NPSA.
10. National Patient Safety Agency (2005) Patient Safety Alert 05: Decreasing the Harm caused by Misplaced Nasogastric Feeding Tubes. London: NPSA.

Appendix 1: Protocol Signature Page

Principal Investigator

Dr. Zvi Grunwald — 3.8.19

Name — Signature — Date

Institution: Thomas Jefferson University

Sponsor Representative

Liron Elia, CEO — 26th of Feb 2019

Name — Signature — Date

Company: ART Healthcare

Appendix 2: Usability Questionnaire

Name of staff member:_____

Position (i.e., nurse, physician, etc.):_____

How would you rank the following tasks on a scale from 1 to 5?

(Circle the response that best represents your opinion)

1. How would you rate the difficulty level of priming and loading the smART System?

1	2	3	4	5
Very Hard	Hard	Average	Easy	Very Easy

2. Over all, how would you rate the operation of the console unit?

1	2	3	4	5
Very Hard	Hard	Average	Easy	Very Easy

3. Over all, how easy was it for you to operate the system?

1	2	3	4	5
Very Hard	Hard	Average	Easy	Very Easy

4. How useful was the system feedback during feeding tube placement?

1	2	3	4	5
Very Bad	Bad	Average	Good	Very Good

5. If an error message occurred during use, how easily was the issue resolved?

1	2	3	4	5
Very Hard	Hard	Average	Easy	Very Easy

6. How would you rate the smART System with respect to "user friendliness"?

1	2	3	4	5
Not Friendly	Somewhat Friendly	Average	Friendly	Very Friendly

7. How satisfied were you with the display and prompts provided by the console?

1	2	3	4	5
Very Unsatisfied	Unsatisfied	Average	Satisfied	Very Satisfied

8. In your opinion based on what you experienced during the study, would you (as the caregiver) how would you rate having the device routinely used in your establishment?

1	2	3	4	5
Very unhelpful	Unhelpful	Average	Beneficial	Very beneficial

9. How satisfied are you with the time it takes to learn how to operate the system (i.e., learning curve)?

1	2	3	4	5
Very Unsatisfied	Unsatisfied	Average	Satisfied	Very Satisfied

10. How easy was it to connect between hospital accessories (feeding bag, IV pole) and smART system?

1	2	3	4	5
Very Hard	Hard	Average	Easy	Very Easy

11. How would you rate the stability of the smART console with respect to the connection to hospital IV pole?

1	2	3	4	5
Very Unstable	Unstable	Average	stable	Very Stable

12. How would you rate the smART console buttons with respect to sensitivity of presses and sufficient illumination?

1	2	3	4	5
Very Bad	Bad	Average	Good	Very Good

13. In your opinion based on your familiarity with other various devices in ICU, how would you rate the device's buzzer and alert volume?

1	2	3	4	5
Very Bad	Bad	Average	Good	Very Good