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Nutrition Monitoring and Feeding Optimization with the smART+ System – Comparative Study

Official Copy

Principal Investigator:	Dr. Ilya Kagan
Investigational Device:	smART+ System
Sponsor:	ART MEDICAL Ltd.

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Rev.	Description of change	Date
01	First issue – created from Comparative study protocol - Sheba (CRO-C-2552 Rev.02)	07-Aug-19
02	Typo fixes, correction to inclusion and exclusion criteria (4.1, 4.2), corrections to the secondary endpoints (2.2), update to the stratified randomization (5.1).	18-Nov-19
03	Typo fixes and minor grammar corrections, Updating the abbreviations list and removing unnecessary Abbreviations Expanding the malnutrition literature review (sec. 1.2.1) Adding to the control group a camera (Nutrition camera) pointed directly at the feeding bottle/bag area (Section 5.3.1) Update data collection lists in sections 5.2.8 and 5.3.5. Add section regarding Comfort-oriented care" (section 7.2) Updating section 10.1.1 regarding the cameras Removing section "study records retention" in section 10.1.2	17-Feb-20
04	sec 2.1- feeding efficiency calculation sec 3.2- extend end of study definition sec 5.2.2- extend the explanation	12-May-20

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05	Updating the abbreviations list and removing unnecessary Abbreviations Collection of breathing information will be done since admission to the ICU (sec. 5.2.8 &5.3.5) Update statistical chapter: Adding calculations explanation expansion (sec. 9). Minor clarifications and minor sentence accuracy throughout the protocol.	
06	Increase no. of subjects at the Beilinson site from 60 to 100.	

Statements of Compliance and Signatures

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.

Principal Investigator

Name	Signature	Date

Institution: _____

Sponsor Representative

Name	Signature	Date

Company: **ART MEDICAL**

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List of Abbreviations

AE	Adverse Event
AKI	Acute kidney injury
cc	Cubic centimeter
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CRF	Case Report Form
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
GRV	Gastric Residual Volume
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IFU	Instructions For Use
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISO	International Organization for Standardization
LOS	Length Of Stay

ml	milliliter
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
NG	Naso-Gastric
PEEP	Positive end expiratory pressure
PI	Principal Investigator
PPI	Proton Pump Inhibitors
QA	Quality Assurance
QC	Quality Control
REE	Resting Energy Expenditure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
VAE	Ventilator Associated Event
APACHE	Acute Physiology and Chronic Health Evaluation

1. Protocol Synopsis

Study Title:	Nutrition Monitoring and Feeding Optimization with the smART+ System
Purpose:	To demonstrate the ability of the smART+ System to optimize the delivery of nutrition
Study Design:	Comparative, prospective, stratified randomization
Study Endpoints:	Primary: Optimization of the delivery of nutrition by the smART+ System as compared to standard of care, by automatically calculating and administering enteral feeding better than standard of care (REE or Calorimeter). Secondary: - Safe use of the entire system (AE/SAE directly related to any of the system components) - Decrease in ICU length of stay from admission to ICU until the decision discharge ordered - Reduction of VAE - Decrease in ventilation days - Decrease in workload related to nurse GRV time - Convenience of use of the system and the user interface (by subjective staff questionnaire) - Assessment of urine flow monitoring related to patient condition and usability
No. of Subjects:	In Beilinson site: 100 patients; 50 patients per group Approximately 200 subjects will be enrolled for the complete multi-center comparative study (100 per group)
Population:	ICU mechanically ventilated patients
Investigational Sites:	Israel, United States, Europe
Principal Investigator:	Dr. Ilya Kagan
Study Duration:	Overall study duration is estimated to enroll for approximately 1 year. Enrollment rate of up to 5 simultaneous patients per site (→ 20 parallel in all 4 sites). Total participation duration: Treatment between 2 days and up to 14 days
Inclusion/Exclusion Criteria:	Inclusion Criteria: - Males and females 18 years or older - Patients that have already been admitted to the ICU (no more than 48 hours before enrollment) - Expected to be ventilated at least 48 hours after enrollment. - Patient requires enteral feeding (by naso/oro-gastric feeding tube)

	Exclusion Criteria: - Pregnant women - Known anatomical anomalies of the nose, oral cavity esophagus or the stomach that may prevent/hinder the ability to insert the feeding tube

1.1. Background

Patients hospitalized in the ICU often lack the inner ability to monitor and check basic functions. It therefore falls onto the shoulders of the medical staff and accompanying devices to take their place and care for the patients.

1.1.1. Reflux detection

Two common techniques for detecting refluxes are Esophageal Impedance Monitoring (EIM) and PH monitoring. Both involve inserting a small tube through the patient's nose into their esophagus and monitored over a period of time. These means are popular in the diagnosis of Gastroesophageal reflux disease (GERD).

1.1.2. Aspiration pneumonia prevention (in the ICU)

Common practice for preventing refluxes and aspiration in tube fed patients in the ICU include: placing the patient in a semi-Fowler's position; feeding at a low and constant rate (~50cc/hr) throughout the day; following the site Gastric Residual Volume (GRV) protocol; flush the catheter after administration of drugs to prevent occlusion; and, administration of Proton Pump Inhibiters (PPIs)[1].

1.1.3. GRV practices

Each site has their own protocol with regard to GRV practice, GRV protocol can vary with regards to the frequency, duration, volume, extraction technique and even what is done with the GRV once extracted.

For example, one site may perform GRV with a 100cc syringe every 4 hours. Promptly returning the suctioned GRV to the patient at the end of the procedure. While another site may connect a bag to the patient's feeding tube and hang it below the height of the patient's bed to slowly empty out the entire content of the patient's stomach over a two hours period, and discard it.

1.1.4. Optimal nutrition

Nutrition for ICU patients is prescribed by a dietitian upon admission based on a manual calculation using the Harris-Benedict equations. Occasionally a calorimeter or REE is implemented, but this is for extreme cases and not continuously monitored.

Regardless of the means used to prescribe the nutrition, GRV and reflux volume are not taken into consideration.

1.1.5. Urine meter

[1] Nutritional Support in ICU Patient. *Pierre Singer*. **ESPEN**.

The most common practice in the field for monitoring urine flow in the ICU is by manually examining the urine collection bag. This is done at best once an hour by a nurse and recorded in the patient's hospital records.

For exceptionally prone patient's there is a growing trend for automatic urine output monitoring. These devices utilize a range of weight-related technologies and provide real time monitoring of urine output and flow rates.

1.2. **The Problems/Study Rationale**

1.2.1. Malnutrition in the ICU

Many critically ill patients develop malnutrition during hospitalization. Malnutrition is a complication which adversely affects clinical outcomes, including length of hospital stay, morbidity, and mortality. The characteristics of ICU patients have changed during the last decade; they now tend to be older and their medical disorders more complex with frequent comorbidities. These factors may contribute to malnutrition in the ICU. Additionally, the combination of stress and undernutrition is associated with negative energy balances and the loss of lean body mass[2].

Mechanically ventilated patients are unable to take food orally and therefore are dependent on enteral nutrition for provision of both energy and protein requirements. Many critically ill patients often have pre-existing conditions, including malnutrition. All of this predisposes patients to nutrition deficits, muscle wasting, delayed wound healing, slower recovery, and increased risk of morbidity and mortality. There is a consensus that supplemental nutrition support is needed and improves outcomes for patients[3].

Providing adequate energy via nutrition support to the mechanically ventilated patient is critical. In the mechanically ventilated patient, overfeeding, even for short periods of time, can lead to hyperglycemia and increases time on the ventilator. Conversely, an increasing caloric deficit (persistent underfeeding) also increases time on the ventilator. Providing early nutritional intervention may shorten hospital stays by 2 days, lower readmission rates by 27% and save $3,800 per patient.

Indirect calorimetry is the recommended method for determining patients' resting energy expenditure (REE). A 2015 estimate showed that only 2% of ICUs were regularly using indirect calorimetry. Predictive equations have therefore been the most commonly practiced method of determining energy needs; however, the literature clearly indicates that each equation has a large potential for error. This makes it difficult to accurately predict an individual patient's energy requirements during critical illness. In general, predictive equations estimate accurately only 50% of the time in ICU patients[4].

[2] Thibault R, Pichard C. Nutrition and clinical outcome in intensive care patients. Curr Opin Clin Nutr Metab Care 2010; 13(2):177-83
[3] Allen, K., Hoffman, L. Enteral Nutrition in the Mechanically Ventilated Patient. Nutr in Clin Pract. Vol 00 2009/1-18. DOI: 10.1002/ncp.10242.
[4] Allen, K., Hoffman, L. Enteral Nutrition in the Mechanically Ventilated Patient. Nutr in Clin Pract. Vol 00 2009/1-18. DOI: 10.1002/ncp.10242.

The American Association for Parenteral and Enteral Nutrition recommends that for patients who are at high risk for malnutrition, efforts should be made to provide >80% of the estimated or calculated energy and protein goal within 48–72 hours, starting with half the patient's calorie goal with the rate slowly increasing over time, in order to achieve the clinical benefit of enteral nutrition over the first week of hospitalization[5]. However, studies have shown that more than 74% of ICU patients failed to receive at least 80% of their proscribed nutrition[6]. Gastric retention and intolerance are usually measured by means of extraction and assessment of the gastric residual volume (GRV). However, the nutrients lost through GRV assessments are often not compensated for. In addition, feeding is regularly paused for medical intervention and imaging occurring outside of the unit.

1.2.2. Neso-gastro (ng) tube positioning

Although generally safe and effective, NG tubes 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. The rate of migration of jejunal placement back to the duodenum or stomach is 27%-42%[7].

It is estimated that approximately 1.2 million feeding tubes are placed each year in the United States alone. 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.

Positioning complications also occur 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.

1.2.3. Aspiration pneumonia

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 preventing or monitoring gastric content aspiration. Many researchers agree that aspiration of gastric contents in tube-fed critically ill patients is of greatest concern.

[5] McClave et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). Jou Par Ent Nutr. Vol 40/2 Feb 2016 156-211. DOI:10.1177/0148607115621863.
[6] Bendavid I, et al., NutritionDay ICU: A 7-year worldwide prevalence study of nutrition practice in intensive care, Clinical Nutrition (2016), http://dx.doi.org/10.1016/j.clnu.2016.07.012.
[7] Feeding Tube Placement: Errors and Complications. *Stayner JL et al*. **Nutr Clin Pract** (2012)

A study on 329 ventilated and tube fed patients from 2010 shows that 88% have at least one instance of gastric content aspiration during the three days monitored[8].

The cost saved per patient per feeding tube: 8K$ (x-ray, GRV, food loss, extended hospital stay).

1.2.4. Acute kidney injury (AKI)

Acute Kidney Injury (AKI) is an umbrella term for any abrupt decrease in Kidney function, encompassing several kidney diseases as well as combinations of such diseases.

Hospital AKI is a significant risk factor for in hospital mortality. It is estimated that AKI affects between 7-18% of hospital inpatients. Among critical ill patient the prevalence goes up to 30-70%. The same study showed that as many as 23.5% cases of hospital AKI went unrecognized.

1.3. **Device Description**

The smART+ is a comprehensive modular patient care system intended for ICU patients. At the heart of the system is the console which stores, compiles and displays data from the different system modules.

Directly connected to the console is the hub, this is a smaller unit that is positioned adjacent to the patient's bed and serves as a mechanical and communications port for the various modules.

The system's modular arrangement allows the flexibility to add modules over time, at this stage the system comprises the following modules:

a) The feeding pump is an integral part of the systems console. The feeding pump is controlled by the console and programed by the user using the console's touch screen.

b) To correspond with the feeding pump, a single use feeding set equipped with an appropriate administration cassette, is loaded into the console.

c) The feeding tube is equipped with sensors that guide the user toward proper placement of the feeding tube without the need of a conformational x-ray. The sensors also detect reflux events and conveys that information to the console. A balloon on the feeding tube's exterior may be inflated at times of reflux in order to hinder the advancement of gastric content in the esophagus and prevent it from reaching the patient's lungs.

d) To relieve pressure and remove access gastric content, a disposable Gastric Residual Volume (GRV) set is connected to the proximal end of the feeding tube. The GRV tube passes through a pinch on the system's hub and is only opened when necessary.

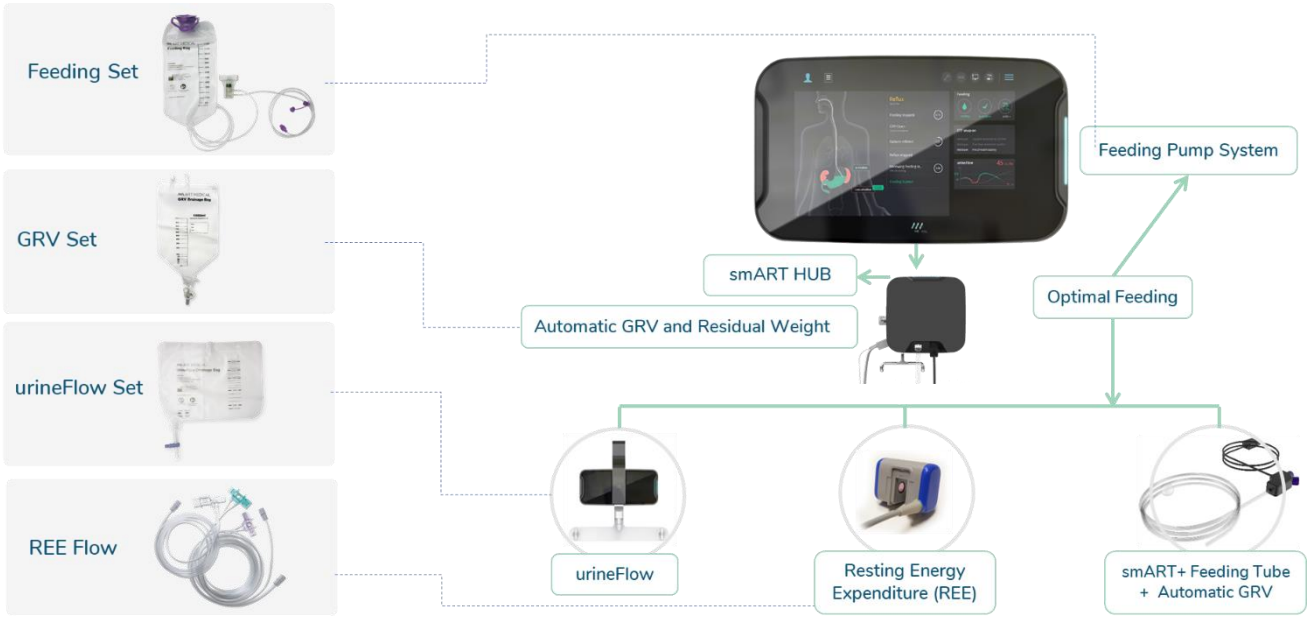
e) The Resting Energy Expenditure (REE) feature is comprised of a disposable flow rate meter and a reusable CO2 detector piece that are added between the patient's endotracheal tube and ventilation tubes. The REE has the capacity to continually measure the patient's energy

[8] Metheny. Effectiveness of an Aspiration Risk-Reduction Protocol. *Norma A*. **Nurs Res** (2010)

expenditure and deduce the patient's nutritional requirements, according to the following equation:

$$REE = \left[3.941\left(\frac{VCO2}{RQ}\right) + 1.11(VCO2)\right]1.44$$

f) The urineFlow disposable set connects to a urinary catheter, relaying urine through a tube and down to a viewing chamber into a collection bag. The viewing chamber is securely inserted into the urineFlow unit which is positioned horizontally off the patient's bed or on an adjacent IV pole. Drops falling through the chamber are captured by a camera mounted in the unit. The images are processed and the drop volumes are calculated and subsequently the patient's urine output rate is monitored. The urineFlow unit also includes a stabilizing mechanism to ensure that the unit is perpendicular to the ground at all times.



1.4. **Intended Use**

Europe: The smART+ System is a feeding optimization system that contains an anti-reflux mechanism, which uses the smART+ Feeding Tube with sensors to prevent gastric content from regurgitating to the esophagus and aspirating into the lungs. The system is intended to be used in healthcare setting.

USA: The smART+ System is a feeding optimization system that contains an anti-reflux mechanism, which uses the smART+ Feeding Tube with sensors and balloon to reduce gastric content from regurgitating to the esophagus. The system is intended to be used in healthcare setting.

1.5. **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.

1.6. Manufacturer and Manufacturing Information

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

1.7. 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

In addition to tube placement, the system allows to obtain REE measurements and calculates the optimized nutritional values required by the patient. Furthermore, the system optimizes feeding by compensating for any lost feeding time or discarded nutritional content that was discarded via the GRV.

1.8. Risk/Benefit Assessment

1.8.1. Known potential risks

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 smART+ disposables that come in any direct or indirect tissue contact.

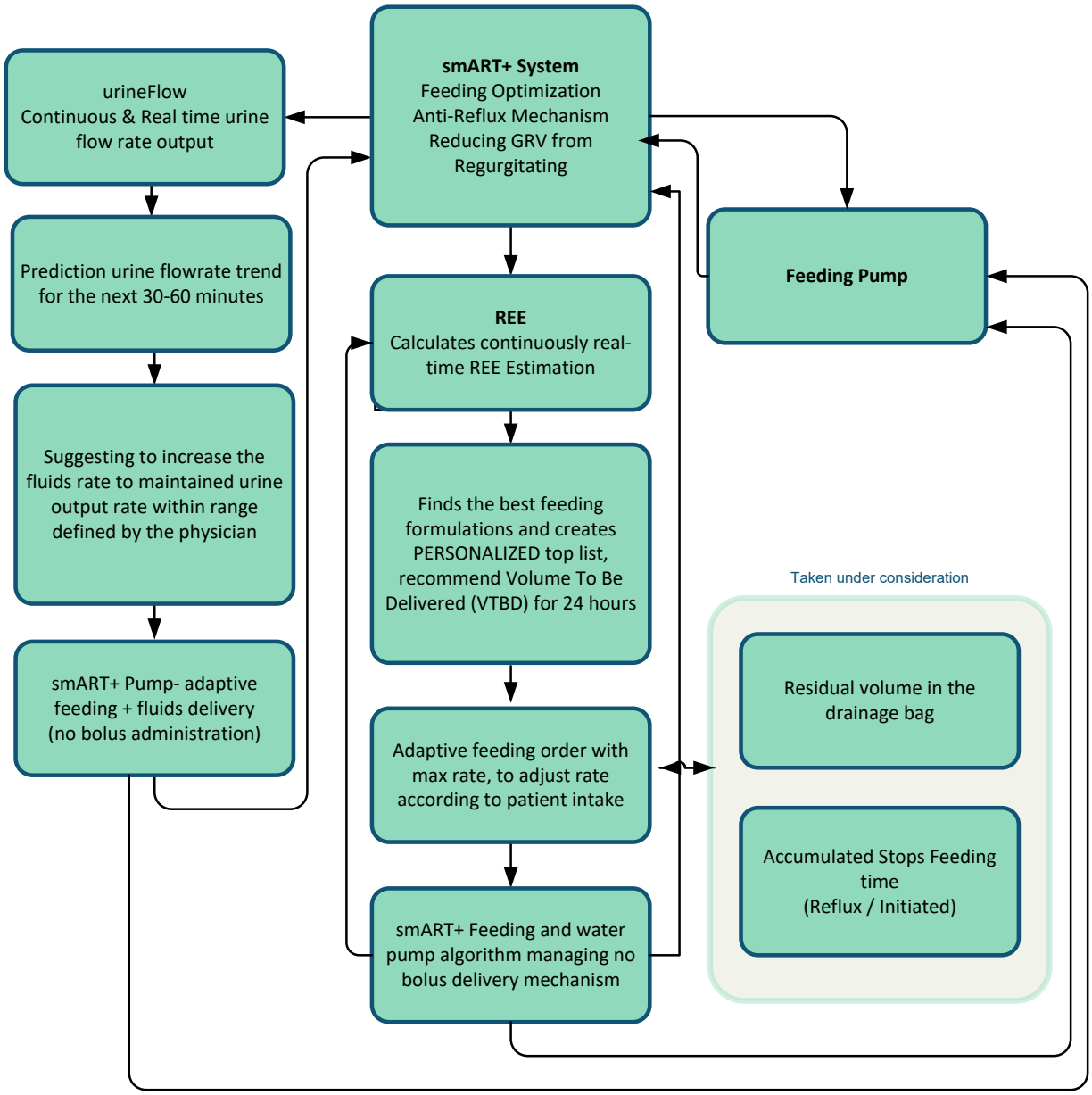
In addition, the results from previous studies supports the company's claim that the insertion, balloon inflation and feeding with the smART™ feeding tube are safe and tolerable. The results also show that the automatic GRV operates properly and efficiently, and the feeding tube device aids in the correct placement of the feeding tube into the patient.

ART Medical 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). The complete risk management document is available from the company upon request.

1.8.2. Known potential benefits

As explained above, the various components of the smART+ System must operate as a cohesive system in order to allow feeding optimization as demonstrated in the flowchart below. With validation of the smART+ 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 risks associated with reflux and aspiration.

In addition, the smART+ System is able to continuously measure the patients REE and minimize the risk of overfeeding. Therefore, by reducing overfeeding it not only achieves feeding optimization, but it also reduces the likelihood of reflux episodes due to overfeeding.



2. Objectives and Endpoints

2.1. **Primary Endpoint:**

Optimization of the delivery of nutrition by the smART+ System as compared to standard of care, by automatically calculating and administering enteral feeding better than standard of care (REE or Calorimeter).

Optimization is defined as the ability of the system to provide adequate nutrition (not overfeed or underfeed) when compared to treatment via standard of care.

Evaluation will be conducted based on an analysis and comparison of the following parameters (obtained through the hospital's electronic records for control group and smART+ records for the treated group):

- Patient caloric target set
- Volume of patient nutritional intake value versus actual patient need – this is calculated by assessing the actual nutrition delivered, discarded nutrition in the GRV bags as well as the unused quantity in discarded feed bottles (if applicable).

As part of optimization evaluation, feeding efficiency calculation ((Net nutrition delivered [ml])/ (VTBD [ml])) should be calculated for the days when the patient received enteral feeding that given under medical order, removed from the patient, or stopped feeding that was not renewed until the end of the study. Feeding efficiency should not be calculated for the days that patient has been discontinued from enteral feeding by a medical order.

2.2. **Secondary Endpoints:**

- Safety

  Safe use of the entire system will be assessed based on the occurrence of device related AE or SAE.

- Decrease in ICU length of stay.

  Measured from admission to ICU until the decision to discharge is ordered.

- Reduction of VAE According to the definition from the latest CDC.
- Decrease in ventilation days.

  Evaluated by the number of hours of etCO2 from the hospital electronic records

- Decrease in workload related to nurse GRV time.

  Patient GRV information obtained through the hospital's electronic records and the usability questionnaires, will be analyzed to determine (a) the estimated nursing time that was expended for GRV activities, and (b) the amounts of GRV removed from the patient.

- Convenience of use of the system and the user interface (by subjective staff questionnaire)

  Evaluated via questionnaires filled by physician users and nurse users participating in the study.

- Assessment of urine flow monitoring related to patient condition and usability

  Patient lab results obtained through the hospital's electronic records and the usability questionnaires, will be analyzed against smART+ system urine alerts, to determine if the alerts will be useful in diagnosis and usability satisfaction.

3. Study Design

3.1. Overall Design

The design of the study is as follows:

- Comparative: 2 groups. 100 participants per group
- Interim statistical analysis: planned after 50 patients
- Random: the randomization is controlled by APACHE score
- Multi-site: Israel, United States, Europe

3.2. End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA).
In addition, participant is considered to have completed the study if he/she is no longer required enteral feeding (due to feeding tube removal, medical order, or any other reason which feeding stopped and is not scheduled to be renewed within the 14 days of study duration).

4. Study Population

4.1. Inclusion Criteria

4.1.1. Males and females 18 years or older
4.1.2. Patients that have already been admitted to ICU (admitted to the ICU for no more than 48 hours before enrollment)
4.1.3. Expected to be ventilated at least 48 hours after enrollments.
4.1.4. Patient requires enteral feeding (by naso/oro-gastric feeding tube)

4.2. Exclusion Criteria

4.2.1. Pregnant women
4.2.2. Known anatomical anomalies of the nose, oral cavity, esophagus or the stomach that may prevent/hinder the ability to insert the feeding tube

4.3. Warnings

- Participants may not receive any kind of nutrition given NOT through the feeding tube (or one of its ports)
- MRI- the Feeding tube should be removed before performing the procedure.
- CPR- the feeding tube should NOT be disconnected from the Hub before performing the procedure.

4.4. Initial Screening

All patients already admitted into the ICU who require enteral feeding may be screened for potential enrollment into the study.

Any study procedure can be performed only following ICF signature process, as approved by the local IRB / EC, and in accordance with GCP.

The following information will be recorded in the study eCRF for each patient found eligible to participate in the study, as part of the initial screening:

- **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.
- **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.
- Inclusion/exclusion criteria

  The initial screening information will be recorded in the eCRF for all patients screened to participate in this study.

4.5. **Screen Failures**

Screen failures are defined as participants who were exanimated by the PI/Co-investigator as part of the initial screening process and were not subsequently entered to the study (e.g., patient found to be ineligible by the PI/Co-investigator, informed consent was not obtained, PI/Co investigator's discretion, etc.).

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes patient demographics, screen failure details, eligibility criteria, and any serious adverse event (SAE).

4.6. **Enrollment**

Patients may be included in the study only if:

- The assessment performed as part of the initial screening (part of the eCRF) is acceptable and patient was found appropriate to participate in the trial, according to the PI (or co-investigator) decision.
- Informed consent has been obtained.
- For women of childbearing age, a negative urine (or blood) pregnancy test.

5. Study Intervention

Following the initial screening procedure and after patient was found to be eligible to participate in the study, patients shall be divided into two study groups:
Group A- ICU patients receiving the investigational device (“Treated”)
Group B- Control group, receiving treatment according to local SOC.
The study intervention describes all study procedures and evaluations to be done as part of the study to support the determination of the primary and secondary objectives outlined in this protocol. Study source documents are defined as data collected from patient's medical chart (recorded in the hospital sources) as well as data collected by the smART+ System, as detailed in sections 5.2.8. and 5.3.5. below. In addition, video recording (as detailed in sections 5.2.1. and 5.3.1.) will be also used for later data analysis and serves as source data.

5.1. Divisions into Groups

After completion of the "initial screening" chapter in the study eCRF recruitment cycle, and after patient was found likely to participate in the trial, patients will randomly be divided into two groups.

Measures to minimize bias: randomization and blinding

Study participants will be randomly assigned to open-label study groups, in randomization ratio of 1:1.

In this current multicenter trial, the randomization procedures will be centrally organized. The ratio between treated and control groups should be balanced on each site.

In order to promote balanced allocation within the groups, the study randomization shall be stratified according to APACHE score measured at baseline.

To avoid possible bias in the selection and allocation of subjects and to ensure that the randomization is properly maintained throughout the trial, a computer randomization algorithm will be used for subject allocation to each group. The randomization algorithm will be part of the eCRF. Randomization will be implemented by the PI/Co-investigator after initial screening of the patient is completed (and before starting study procedures).

This will allow first of all the selection of suitable patients, and only then division into groups.

5.2. Group A- Interventional Device ("Treated")

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

5.2.1. Videotaping of subject- group A

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 behind/near the patient head, allowing recording of movements of the feeding tube and medical procedures for later comparison with the data logs recorded by the smART+ console. All recorded data must be attached to the patient files and serves as an integral part of the analyzable data for the study. The video recording is not binding and the PI or the sponsor may choose not to video a specific patient at certain times or at all.

5.2.2. Connecting the patient to the smART+ System

The patient should be connected up to all applicable modules of the smART+ as soon as possible after being enrolled in the study. Connection and use of the smART+ UrineFlow system will be as needed according to PI decision.

Detailed instructions of how to connect a patient to the system can be found in the smART+ User Manual and the accompanying Quick Guides.

5.2.3. Feeding insertion- group A

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 according to hospital procedures (such as abdominal /chest X-ray /other gold standard).

5.2.4. Vital signs- group A

Vital signs (e.g., temperature, pulse, respirations, blood pressure) should be noted within 10 minutes of feeding tube insertion.

5.2.5. REE measurement- group A

Once the patient has recovered from the process of inserting the feeding tube, a baseline REE measurement should be taken using the smART+ flow sensor and CO_2 sensor.

5.2.6. Feeding program- group A

Once the REE measurement is accomplished, personnel authorized by the hospital should program a suitable feeding program using the smART+ Console and in accordance with hospital procedure.

5.2.7. Ongoing use- group A

If system alerts of tube displacement during ongoing use, the need for tube reinsertion/repositioning should be evaluated and performed as needed.

If system alerts an increase in REE, the message should be evaluated by personnel authorized by the hospital, who should decide if to change the patient's feeding program.

5.2.8. Data recording- group A

The following information will be acquired from the patient's medical chart (recorded in the hospital sources) into the eCRF, for each patient

- Initial screening: as detailed in the study eCRF
- Feeding information: Food types, amounts, rate, water delivery, parenteral nutrition, TPN, other nutritional data
- Gastric residual volume: discard gastric residuals amount, GRV procedure times.
- Medications provided: as detailed in the study eCRF.
- Lab results: patient lab results, as detailed in the study eCRF, and obtained 24 hours prior the feeding tube insertion and during the study, should be recorded in the eCRF.
- Imaging: (X-ray, CT, and alike) performed during the study should be obtained and attached to the eCRF.
- Urine: amounts, rates, times, warnings
- ICU submission and discharge ordering times
- Breathing data reports starting from the ICU admission (FiO2, PEEP)
- Demographics

The following information will be recorded by the smART+ console (or accompanying recording equipment) and extracted directly by the sponsor:

- Urine monitoring: amounts, rates, times, warnings, trends (and all other data collected by the smART+ System).
- Feeding information: Food types, amounts, rate, fluids delivery (and all other data collected by the smART+ System).
- Gastric residual volume: GRV amounts and times
- Reflux and position data
- REE data
- Breathing data (collected by the smART+ System)
- All other data collected by the smART+ System.

5.2.9. Staff Questionnaires - group A

At the end of the study, staff will be required to complete a usability questionnaire assessing the convenience of using the system and the user interface. Two different questionnaires will be used for either physician users and nurse users participating in the study. The questionnaires will include a variety of questions such as YES/NO, open-ended and scoring-based questions.

5.3. **Group B- Control Group**

5.3.1. Nutrition camera - group B

Local site procedure for changing feeding bottle/bag should be followed as needed and according to hospital procedures. An additional camera (Nutrition camera) will be added, pointed directly at the feeding bottle/bag area and not on the patient.

The Nutrition camera will record a real time video and automatically save it in storage device (such as PC). This camera captures the amount of feeding discarded that was not used for patient feeding. It will allow later data analyzation to quantify the amount of feeding discarded by using the grid lines marked on the feeding bag's/bottle's exterior. In order to ensure the effectiveness of the Nutrition camera, it will bear an instruction such as Ensure camera points at feeding bottle/bag.

5.3.2. REE or calorimeter measurement- group B

Once the patient is enrolled in the study a baseline REE or calorimeter measurement (according to gold standard in the department) should be taken using available department equipment.

5.3.3. Feeding program - group B

Once the REE \ calorimeter measurement \ other method to determined caloric target is obtained, personnel authorized by the hospital should administer a suitable feeding program per hospital standard of care (i.e., hospital's usual available feeding tubes, feeding pumps, gravity feeding, etc.).

5.3.4. On-going treatment- group B

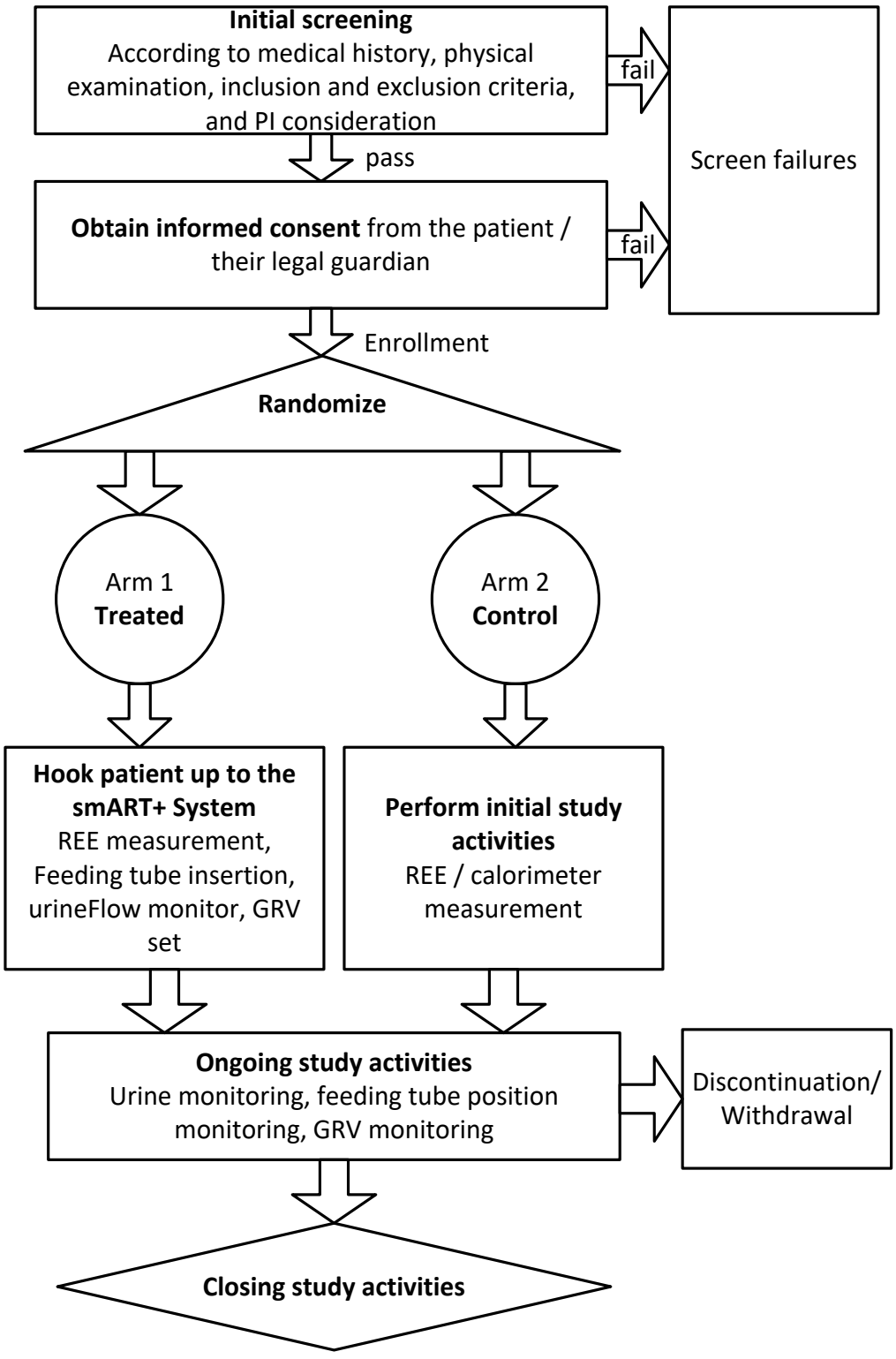
Patients in the control group should be treated in accordance with standard hospital procedures per usual hospital/physician determined treatment plan.

5.3.5. Data recording- group B

The following information will be acquired from the patient's medical chart (recorded in the hospital sources) for each patient:

- Initial screening: as detailed in the study eCRF
- Feeding information: Food types, amounts, rate, water delivery, parenteral nutrition, TPN, Indirect calorimeter and other nutritional data.
- Gastric residual volume: discard gastric residuals amount, GRV procedure times.
- Medications provided: as detailed in the study eCRF.
- Lab results: all patient lab results ordered during the study as well as all available lab results obtained 24 hours prior to study enrollment and added to the eCRF.
- Imaging: patient imaging (X-rays, CT, and alike) performed during the study should be obtained and added to the eCRF.
- Urine monitoring: amounts, rates, times, warnings and all data related to urinary output and diagnosis, and found in the hospital source.
- ICU submission and discharge ordering times
- Breathing data reports starting from the ICU admission (FiO2, PEEP)
- Demographics

5.4. **Study Flowchart**



5.5. **Schedule of Activities (SoA)**

Procedures	Screening/ enrollment	Medical Device Placement	Ongoing use	Termination
Day	1	1(T)	Up to 14	1 up to 14
Informed Consent	T+C			
Eligibility Criteria	T+C			
Physical Exam	T+C			
Pregnancy test (if applicable)	T+C			
Videotaping		T+C	T+C	
Vital Signs		T+C	T+C	T+C
REE or calorimeter/spirometer measurement		T+C	T as needed and according to procedures	
Lab Data			T+C	T*+C*
Medical Device Administration		T	T	
GRV Measurements			T+C as needed and according to procedures	
Urine monitoring			T as needed and according to procedures	
Adverse Events	T+C	T+C	T+C	T+C
Concomitant Medication		T+C	T+C	T+C
Information regarding nutritional supplement administration		T+C	T+C	

T – group A – "Treated"
C – group B – "Control"
* - For T only – obtained retroactively 24 hours prior the feeding tube insertion and during the ongoing study

6. Preparation/Handling/Storage/Accountability

6.1. Acquisition and accountability

All disposables and capital equipment will be provided to the investigator directly by the sponsor.

The site will store the capital equipment throughout the entire period of the trial.

The disposables will be delivered to the sites (in quantities or in individuals) according to the enrollment rate. The sponsor will ensure that the site has a sufficient amount of equipment (capital

and disposable) for replacement of damaged equipment/parallel experiments/additional participants.

Device Receipt logs will be updated accordingly.

6.2. Used/unused devices

Used disposable devices will be discarded after opening/ use according to hospital procedures. Accountability logs will be updated accordingly.

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

6.3. Packaging and labeling

smART+ System information can be obtained from the:

- Investigator brochure (IB)
- Package or device labeling/instruction for use (IFU)
- Device quick guides
- User manual

7. Study Discontinuation and Participant Discontinuation/Withdrawal

7.1. Participant Discontinuation/Withdrawal from The Study

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 discontinuation/withdrawal:

- The insertion of the feeding tube has failed after 3 attempts in each nostril
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

In the event a subject discontinuation/withdraws from the study the following procedures will be observed:

- The reasons for any subject discontinuation/withdrawal will be recorded on the study completion form of the eCRF.
- The investigator will inform the sponsor 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.

Subjects who signed the informed consent form and are randomized but do not received the study intervention are considered screen failures and may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study may also be replaced.

In addition, this study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause.

Circumstances that may warrant termination or suspension include according to the PI decision, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

7.2. **Medical condition resulted in the decision to deliver "Comfort-oriented care"**

If during the study patient's medical condition changed and the decision/preferences is NOT to receive aggressive, life-sustaining treatments but to delivered comfort-oriented care (or equivalent according to hospital policy and PI confirmation), subject should be terminated from the study.

If in this case the smART+ feeding tube cannot be removed (since a tube must be kept for drainage purposes and a new tube should not be inserted), the feeding tube can continue to be used for drainage / other treatment purposes under the comfort-oriented care.

Although in this case the smART+ feeding tube can be left inside the patient, it must be disconnected from the smART+ device (and all other smART+ components).

7.3. **Follow-Up**

No follow-up will be conducted for this study. AE and SAE collection is to be conducted up until the moment the subject study participation is terminated. AEs and SAEs occurring after study termination are not to be collected or reported for the purpose of this study.

7.4. **Adverse Events and Serious Adverse Events**

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during filling of the eCRF, treatments/other medical procedures or upon review by a study monitor.

7.4.1.Adverse events (AE)

AE DEFINITION

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

NOTE 1- This includes any event that is a result of a use error or intentional misuse.

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.

AE CLASSIFICATION AND REPORTING

Group A- Interventional Device

All AEs will be recorded on the adverse events page of the eCRF. AEs will be recorded after the subject (or delegate) has signed the informed consent and throughout the study. Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. AE reporting and documentation will be discontinued, at the end of the study, immediately after feeding tube removal.

Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring during the study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Severity and relationship to study device will be assigned by the investigator as described below.

All adverse events will be graded for severity as follows:

- Mild: Events, sign or symptom, usually transient, requiring minimal or no special treatment and generally not interfering with participant's usual activities.
- Moderate: Events, sign or symptom, which may be ameliorated by simple therapeutic measures; yet, may interfere with usual activity.
- Severe: Events, sign or symptom that are intense or debilitating and that interfere with usual activities. Recovery is usually aided by therapeutic measures.

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **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.

Group B- Control Group

AEs recorded for group B should include only related or could affect (according to PI decision) the patient's medical condition that related to urine, feeding, GRV and REE.

7.4.2.Serious Adverse Events (SAE)

SAE DEFINITION

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.

SAE REPORTING

Due to the complex clinical status of the patients a very large number of AEs and SAEs occur; therefore, ***only device related SAEs will be reported to the IRB / local ethic committee***.

This is in line with information provided in FDA guidance document “Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs - Improving Human Subject Protection”. Per the guidance and the IDE regulation, reportable events to the IRB are: “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 investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.”

The guidance further states: “Sponsors can assess the implications and significance of AE reports promptly and are required to report serious, unexpected events associated with the use of a drug or device, including analyses of such events, to investigators and to FDA. In addition, sponsors are required to report analyses of unexpected adverse device experiences to IRBs.”

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as

possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

Accompanying documentation, such as copies of hospital case reports, autopsy report, and other documents when applicable, should be sent to the sponsor as soon as they are available.

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

7.4.3. Expected / anticipated adverse events

Expected/anticipated adverse events are AEs that are known to occur for the study intervention being studied and should be collected and recorded in the study eCRF (as other AEs).

<u>Anticipated adverse events associated with the insertion and presence of feeding tubes include:</u>

- 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 feeding tube.
- Nausea and vomiting
- Pneumothorax

Anticipated adverse events associated with feeding are:

- Abdominal discomfort and pain
- Abdominal bloating
- Diarrhea

The study PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Expected/anticipated adverse events will be reported in the study eCRF and marked as "Expected/anticipated adverse events".

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 MEDICAL 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.
The investigational site will provide to the monitor direct access to the trial related source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

9. Statistical Considerations

9.1 Sample size consideration

Approximately 200 subjects will be enrolled for the complete multi-center comparative study (100 per group). An interim analysis will be performed after 100 subjects (50 in each group) are enrolled on the primary endpoint.

1- **Based on the primary endpoint at interim analysis (feeding efficiency):**

Sample size rationale:

The rationale for sample size calculation is based on a difference in feeding efficiency between the tested group (with smART+ System) and the current standard practice (group B).

Sample size justification:

The comparison between groups of food consumption estimations is reflected by Effect size, calculated as the difference between the groups normalized by the common standard deviation.
The calculation uses the following formulation: (Estimation in the tested group - Estimation in control group)/Common standard deviation [Error! Bookmark not defined.,Error! Bookmark not defined.].

A sample size of 50 in each group will have 90% power to detect an **effect size of 0.70** using a two-group t-test with a 0.025 two-sided significance level. [1, 2]
A significance of 0.025 was used instead of the usual 0.05 (alpha adjustment) due to the increase in the chance of making a Type 1 error following two subsequent analysis.

2- Based on the secondary endpoints at end of study:

2.1 Ventilation days:

Sample size rationale:

The rationale for sample size calculation is based on a difference in Ventilation days between the tested group (with smART+ System) and the current standard practice (group B).

Sample size justification:
The comparison between groups in ventilation days is reflected by Effect size.
A sample size of 100 in each group will have 90% power to detect an **effect size of 0.46** using a two group t-test with a 0.05 two-sided significance level. [1, 2]

2.2 Ventilation Associated Events:

Sample size rationale:
The rationale for sample size calculation is based on a difference in the proportion of subjects with Ventilation-Associated Events between the tested group (with smART+ System) and the current standard practice (group B) of 20%.

Sample size justification:
A two group continuity corrected c^2 test with a 0.05 two-sided significance level will have 90% power to detect the difference between a Group 1 proportion, p_1, and a Group 2 proportion, p_2 (**odds ratio of 2.70**) when the sample size in each group is 100.[3]

2.3 Length of stay:

Sample size rationale:
The rationale for sample size calculation is based on a difference in length of stay between the tested group (with smART+ System) and the current standard practice (group B).

Sample size justification:
The comparison between groups in ventilation days is reflected by Effect size.
A sample size of 100 in each group will have 90% power to detect an **effect size of 0.46** using a two group t-test with a 0.05 two-sided significance level. [1, 2]

References:
1. Dixon, W.J., Massey, F.J. **Introduction to Statistical Analysis. 4th Edition** McGraw-Hill (1983)
2. O'Brien, R.G., Muller, K.E. **Applied Analysis of Variance in Behavioral Science** Marcel Dekker, New York (1983) pp. 297-344
3. Fleiss, J.L., Tytun, A., Ury, S.H.K. "A simple approximation for calculating sample sizes for comparing independent proportions" *Biometrics* 36(1980) pp. 343-346

9.2 Endpoints analysis:

9.2.1 General:

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics.

For categorical variables summary tables will be provided giving sample size, absolute and relative frequency and 95% CI (Confidence Interval) for proportions by study arm.
For continuous variables summary tables will be provided giving sample size, arithmetic mean, standard deviation, coefficient of variation (CV%), median, minimum and maximum and 95% CI (Confidence Interval) for means of variables by study arm.
All tests will be two-tailed, and a p value of 5% or less will be considered statistically significant.
The data will be analyzed using the SAS ® version 9.4 (SAS Institute, Cary North Carolina).

9.2.2 Primary endpoint:

The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference in feeding efficiency between the study groups.

9.2.3 Secondary endpoints:

- The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference in number of ventilation days (Evaluated by the number of hours of etCO2 from the hospital electronic records) between the study groups.
- The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference in the estimated nursing time that was expended for GRV activities, and the amounts of GRV removed from the patient between the study groups.
- Convenience of use of the system and the user interface scores (by subjective staff questionnaire) will be summarized in an appropriate table by study group
- The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference in the assessment of urine flow monitoring related to patient condition and usability between the study groups.
- The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference in ICU length of stay (measured from admission to ICU until the decision to discharge is ordered) between the study groups.
- Chi-square test or Fisher's Exact test (as is appropriate) will be applied for testing the statistical significance of the difference in percent of subjects experiencing Ventilation associated events between the study groups.

9.2.5 Safety:

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, most updated version) terminology and presented in tables by System Organ Class (SOC) and Preferred Term (PT).

AE data will be listed individually and summarized by SOC and by PT within a system organ class for each study group.
Frequency of TEAEs (Treatment-Emergent Adverse Events) and device-related adverse events will be summarized in tables by SOC, PT and study group and by seriousness.
Chi-square test or Fisher's Exact test (as is appropriate) will be applied for testing the statistical significance of the difference in percent of subjects experienced any AE, drug-related AE and SAE between the study groups.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.

10. Regulatory, Ethical, and Study Oversight Considerations

10.1. Informed Consent Process and Documentation

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.

Informed consent process is initiated prior to the individual’s participation in the study and continues throughout the individual’s study participation. Consent forms will be Institutional Review Board (IRB)-approved and the patient/patient representative will be asked to read and review the document prior to starting intervention. The investigator will explain the research study to the patient/patient representative and answer any questions that may arise. A verbal explanation will be provided in terms suited to the patient/patient representative comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. patient/patient representative will have the opportunity to carefully review the written consent form and ask questions prior to signing. The patient/patient representative should have the opportunity to discuss the study with their family or think about it prior to agreeing to participate. The participant (or a legal representative on their behalf) will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the patient/patient representative for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.1. Confidentiality and privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover all the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict

confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible. As previously mentioned, during the study, a video recording of the treated patient (group A) is obtained. The camera will be placed behind/near the patients' head, allowing recording of movements of the feeding tube and medical procedures, without revealing the identity of the patient.

As mention above, in the control group (group B), a Nutrition camera will be placed pointed at feeding bottle/bag area, without revealing the identity of the patient.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored safely by the sponsor. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the research staff will be secured and password protected.

10.1.2. Data collection and management responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data from each subject will be recorded as part of the routine data collection & recording, in the hospital source documents or (but not limited to) in the patient's medical charts (as accepted in the department). Later, the data will be transferred by the investigator to the eCRFs supplied by the sponsor. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Quality check for errors and omissions will be performed to ensure the accuracy of the entered data.

The eCRF should be completed in full, i.e., no fields should be left blank once the subject has completed the study. The investigator must review the eCRFs for completeness and accuracy and must sign/date the forms where indicated. The investigator shall retain

originals of eCRFs, subject consent forms, and study data as permanent records for the period indicated under "STUDY RECORD RETENTION" below.

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

10.1.3. Protocol deviations

Noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Any deviations from the study protocol should be reported to the sponsor and documented on study deviation forms. Further details about the handling of protocol deviations will be included in the study SOP/MOP.

10.1.4. Publication and data sharing policy

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

10.1.5. Conflict of interest policy

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

11. Resources:

[1] Code of Federal Regulations (CFR)

- 21 CFR Part 11: Electronic Records, Electronic Signatures
- 21 CFR Part 50: Protection of Human Subjects
- 21 CFR Part 54: Financial Disclosure by Clinical Investigators
- 21 CFR Part 56: Institutional Review Boards
- 21 CFR Part 812: Investigational Device Exemptions
- 42 CFR Part 11: Clinical Trial Registration and Results Information Submission

[2] Food and Drug Administration (FDA)

- Compliance Actions and Activities
- FDA Regulations Relating to Good Clinical Practice and Clinical Trials
- Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs – Improving Human Subject Protection
- Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees
- Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance
- Guidance for Industry: Electronic Source Data in Clinical Investigations
- Guidance for Industry: Multiple Endpoints in Clinical Trials
- Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring

- Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications
- Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Standardized Study Data
- Guidance for Industry: Safety Assessment for IND Safety Reporting

[3] Department of Health and Human Services (HHS)
- The HIPAA Privacy Rule
- HIPAA Privacy Rule: Information for Researchers

[4] ISO 14155:2011 - Clinical Investigation of Medical Devices for Human Subjects -- Good Clinical Practice

[5] Israel's Health Department procedure for the conduct of clinical trials: https://www.health.gov.il/hozer/DR_14.pdf

12. References

Footnotes in the relevant places along the document.

Nutrition Monitoring and Feeding Optimization with the smART+ System – Comparative Study

Principal Investigator:	Dr. Ilya Kagan
Investigational Device:	smART+ System
Sponsor:	ART MEDICAL Ltd.

Approvals:

	Name	Title	Signature	Date
Issued by	Shirly Steinlauf	Head of CA, RA & QA		
Review by	Bosmat Friedman	RA consultant		
Approved by	Liron Elia	CEO		

Change History:

Rev.	Description of change	Date
01	First issue – created from Comparative study protocol - Sheba (CRO-C-2552 Rev.02)	07-Aug-19
02	Typo fixes, correction to inclusion and exclusion criteria (4.1, 4.2), corrections to the secondary endpoints (2.2), update to the stratified randomization (5.1).	18-Nov-19
03	Typo fixes and minor grammar corrections, Updating the abbreviations list and removing unnecessary Abbreviations Expanding the malnutrition literature review (sec. 1.2.1) Adding to the control group a camera (Nutrition camera) pointed directly at the feeding bottle/bag area (Section 5.3.1) Update data collection lists in sections 5.2.8 and 5.3.5. Add section regarding Comfort-oriented care" (section 7.2) Updating section 10.1.1 regarding the cameras Removing section "study records retention" in section 10.1.2	17-Feb-20
04	sec 2.1- feeding efficiency calculation sec 3.2- extend end of study definition sec 5.2.2- extend the explanation	12-May-20

05	Updating the abbreviations list and removing unnecessary Abbreviations Collection of breathing information will be done since admission to the ICU (sec. 5.2.8 &5.3.5) Update statistical chapter: Adding calculations explanation expansion (sec. 9). Minor clarifications and minor sentence accuracy throughout the protocol.	
06	Increase no. of subjects at the Beilinson site from 60 to 100.	

Statements of Compliance and Signatures

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.

Principal Investigator

Name	Signature	Date

Institution: _____

Sponsor Representative

Name	Signature	Date

Company: **ART MEDICAL**

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List of Abbreviations

AE	Adverse Event
AKI	Acute kidney injury
cc	Cubic centimeter
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CRF	Case Report Form
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
GRV	Gastric Residual Volume
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IFU	Instructions For Use
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISO	International Organization for Standardization
LOS	Length Of Stay

ml	milliliter
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
NG	Naso-Gastric
PEEP	Positive end expiratory pressure
PI	Principal Investigator
PPI	Proton Pump Inhibitors
QA	Quality Assurance
QC	Quality Control
REE	Resting Energy Expenditure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
VAE	Ventilator Associated Event
APACHE	Acute Physiology and Chronic Health Evaluation

1. Protocol Synopsis

Study Title:	Nutrition Monitoring and Feeding Optimization with the smART+ System
Purpose:	To demonstrate the ability of the smART+ System to optimize the delivery of nutrition
Study Design:	Comparative, prospective, stratified randomization
Study Endpoints:	Primary: Optimization of the delivery of nutrition by the smART+ System as compared to standard of care, by automatically calculating and administering enteral feeding better than standard of care (REE or Calorimeter). Secondary: - Safe use of the entire system (AE/SAE directly related to any of the system components) - Decrease in ICU length of stay from admission to ICU until the decision discharge ordered - Reduction of VAE - Decrease in ventilation days - Decrease in workload related to nurse GRV time - Convenience of use of the system and the user interface (by subjective staff questionnaire) - Assessment of urine flow monitoring related to patient condition and usability
No. of Subjects:	In Beilinson site: 100 patients; 50 patients per group Approximately 200 subjects will be enrolled for the complete multi-center comparative study (100 per group)
Population:	ICU mechanically ventilated patients
Investigational Sites:	Israel, United States, Europe
Principal Investigator:	Dr. Ilya Kagan
Study Duration:	Overall study duration is estimated to enroll for approximately 1 year. Enrollment rate of up to 5 simultaneous patients per site (→ 20 parallel in all 4 sites). Total participation duration: Treatment between 2 days and up to 14 days
Inclusion/Exclusion Criteria:	Inclusion Criteria: - Males and females 18 years or older - Patients that have already been admitted to the ICU (no more than 48 hours before enrollment) - Expected to be ventilated at least 48 hours after enrollment. - Patient requires enteral feeding (by naso/oro-gastric feeding tube)

	Exclusion Criteria: - Pregnant women - Known anatomical anomalies of the nose, oral cavity esophagus or the stomach that may prevent/hinder the ability to insert the feeding tube

1.1. Background

Patients hospitalized in the ICU often lack the inner ability to monitor and check basic functions. It therefore falls onto the shoulders of the medical staff and accompanying devices to take their place and care for the patients.

1.1.1. Reflux detection

Two common techniques for detecting refluxes are Esophageal Impedance Monitoring (EIM) and PH monitoring. Both involve inserting a small tube through the patient's nose into their esophagus and monitored over a period of time. These means are popular in the diagnosis of Gastroesophageal reflux disease (GERD).

1.1.2. Aspiration pneumonia prevention (in the ICU)

Common practice for preventing refluxes and aspiration in tube fed patients in the ICU include: placing the patient in a semi-Fowler's position; feeding at a low and constant rate (~50cc/hr) throughout the day; following the site Gastric Residual Volume (GRV) protocol; flush the catheter after administration of drugs to prevent occlusion; and, administration of Proton Pump Inhibiters (PPIs)[1].

1.1.3. GRV practices

Each site has their own protocol with regard to GRV practice, GRV protocol can vary with regards to the frequency, duration, volume, extraction technique and even what is done with the GRV once extracted.

For example, one site may perform GRV with a 100cc syringe every 4 hours. Promptly returning the suctioned GRV to the patient at the end of the procedure. While another site may connect a bag to the patient's feeding tube and hang it below the height of the patient's bed to slowly empty out the entire content of the patient's stomach over a two hours period, and discard it.

1.1.4. Optimal nutrition

Nutrition for ICU patients is prescribed by a dietitian upon admission based on a manual calculation using the Harris-Benedict equations. Occasionally a calorimeter or REE is implemented, but this is for extreme cases and not continuously monitored.

Regardless of the means used to prescribe the nutrition, GRV and reflux volume are not taken into consideration.

1.1.5. Urine meter

[1] Nutritional Support in ICU Patient. *Pierre Singer*. **ESPEN**.

The most common practice in the field for monitoring urine flow in the ICU is by manually examining the urine collection bag. This is done at best once an hour by a nurse and recorded in the patient's hospital records.

For exceptionally prone patient's there is a growing trend for automatic urine output monitoring. These devices utilize a range of weight-related technologies and provide real time monitoring of urine output and flow rates.

1.2. **The Problems/Study Rationale**

1.2.1. Malnutrition in the ICU

Many critically ill patients develop malnutrition during hospitalization. Malnutrition is a complication which adversely affects clinical outcomes, including length of hospital stay, morbidity, and mortality. The characteristics of ICU patients have changed during the last decade; they now tend to be older and their medical disorders more complex with frequent comorbidities. These factors may contribute to malnutrition in the ICU. Additionally, the combination of stress and undernutrition is associated with negative energy balances and the loss of lean body mass[2].

Mechanically ventilated patients are unable to take food orally and therefore are dependent on enteral nutrition for provision of both energy and protein requirements. Many critically ill patients often have pre-existing conditions, including malnutrition. All of this predisposes patients to nutrition deficits, muscle wasting, delayed wound healing, slower recovery, and increased risk of morbidity and mortality. There is a consensus that supplemental nutrition support is needed and improves outcomes for patients[3].

Providing adequate energy via nutrition support to the mechanically ventilated patient is critical. In the mechanically ventilated patient, overfeeding, even for short periods of time, can lead to hyperglycemia and increases time on the ventilator. Conversely, an increasing caloric deficit (persistent underfeeding) also increases time on the ventilator. Providing early nutritional intervention may shorten hospital stays by 2 days, lower readmission rates by 27% and save $3,800 per patient.

Indirect calorimetry is the recommended method for determining patients' resting energy expenditure (REE). A 2015 estimate showed that only 2% of ICUs were regularly using indirect calorimetry. Predictive equations have therefore been the most commonly practiced method of determining energy needs; however, the literature clearly indicates that each equation has a large potential for error. This makes it difficult to accurately predict an individual patient's energy requirements during critical illness. In general, predictive equations estimate accurately only 50% of the time in ICU patients[4].

[2] Thibault R, Pichard C. Nutrition and clinical outcome in intensive care patients. Curr Opin Clin Nutr Metab Care 2010; 13(2):177-83
[3] Allen, K., Hoffman, L. Enteral Nutrition in the Mechanically Ventilated Patient. Nutr in Clin Pract. Vol 00 2009/1-18. DOI: 10.1002/ncp.10242.
[4] Allen, K., Hoffman, L. Enteral Nutrition in the Mechanically Ventilated Patient. Nutr in Clin Pract. Vol 00 2009/1-18. DOI: 10.1002/ncp.10242.

The American Association for Parenteral and Enteral Nutrition recommends that for patients who are at high risk for malnutrition, efforts should be made to provide >80% of the estimated or calculated energy and protein goal within 48–72 hours, starting with half the patient's calorie goal with the rate slowly increasing over time, in order to achieve the clinical benefit of enteral nutrition over the first week of hospitalization[5]. However, studies have shown that more than 74% of ICU patients failed to receive at least 80% of their proscribed nutrition[6]. Gastric retention and intolerance are usually measured by means of extraction and assessment of the gastric residual volume (GRV). However, the nutrients lost through GRV assessments are often not compensated for. In addition, feeding is regularly paused for medical intervention and imaging occurring outside of the unit.

1.2.2. Neso-gastro (ng) tube positioning

Although generally safe and effective, NG tubes 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. The rate of migration of jejunal placement back to the duodenum or stomach is 27%-42%[7].

It is estimated that approximately 1.2 million feeding tubes are placed each year in the United States alone. 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.

Positioning complications also occur 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.

1.2.3. Aspiration pneumonia

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 preventing or monitoring gastric content aspiration. Many researchers agree that aspiration of gastric contents in tube-fed critically ill patients is of greatest concern.

[5] McClave et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). Jou Par Ent Nutr. Vol 40/2 Feb 2016 156-211. DOI:10.1177/0148607115621863.
[6] Bendavid I, et al., NutritionDay ICU: A 7-year worldwide prevalence study of nutrition practice in intensive care, Clinical Nutrition (2016), http://dx.doi.org/10.1016/j.clnu.2016.07.012.
[7] Feeding Tube Placement: Errors and Complications. *Stayner JL et al*. **Nutr Clin Pract** (2012)

A study on 329 ventilated and tube fed patients from 2010 shows that 88% have at least one instance of gastric content aspiration during the three days monitored[8].

The cost saved per patient per feeding tube: 8K$ (x-ray, GRV, food loss, extended hospital stay).

1.2.4. Acute kidney injury (AKI)

Acute Kidney Injury (AKI) is an umbrella term for any abrupt decrease in Kidney function, encompassing several kidney diseases as well as combinations of such diseases.

Hospital AKI is a significant risk factor for in hospital mortality. It is estimated that AKI affects between 7-18% of hospital inpatients. Among critical ill patient the prevalence goes up to 30-70%. The same study showed that as many as 23.5% cases of hospital AKI went unrecognized.

1.3. **Device Description**

The smART+ is a comprehensive modular patient care system intended for ICU patients. At the heart of the system is the console which stores, compiles and displays data from the different system modules.

Directly connected to the console is the hub, this is a smaller unit that is positioned adjacent to the patient's bed and serves as a mechanical and communications port for the various modules.

The system's modular arrangement allows the flexibility to add modules over time, at this stage the system comprises the following modules:

a) The feeding pump is an integral part of the systems console. The feeding pump is controlled by the console and programed by the user using the console's touch screen.

b) To correspond with the feeding pump, a single use feeding set equipped with an appropriate administration cassette, is loaded into the console.

c) The feeding tube is equipped with sensors that guide the user toward proper placement of the feeding tube without the need of a conformational x-ray. The sensors also detect reflux events and conveys that information to the console. A balloon on the feeding tube's exterior may be inflated at times of reflux in order to hinder the advancement of gastric content in the esophagus and prevent it from reaching the patient's lungs.

d) To relieve pressure and remove access gastric content, a disposable Gastric Residual Volume (GRV) set is connected to the proximal end of the feeding tube. The GRV tube passes through a pinch on the system's hub and is only opened when necessary.

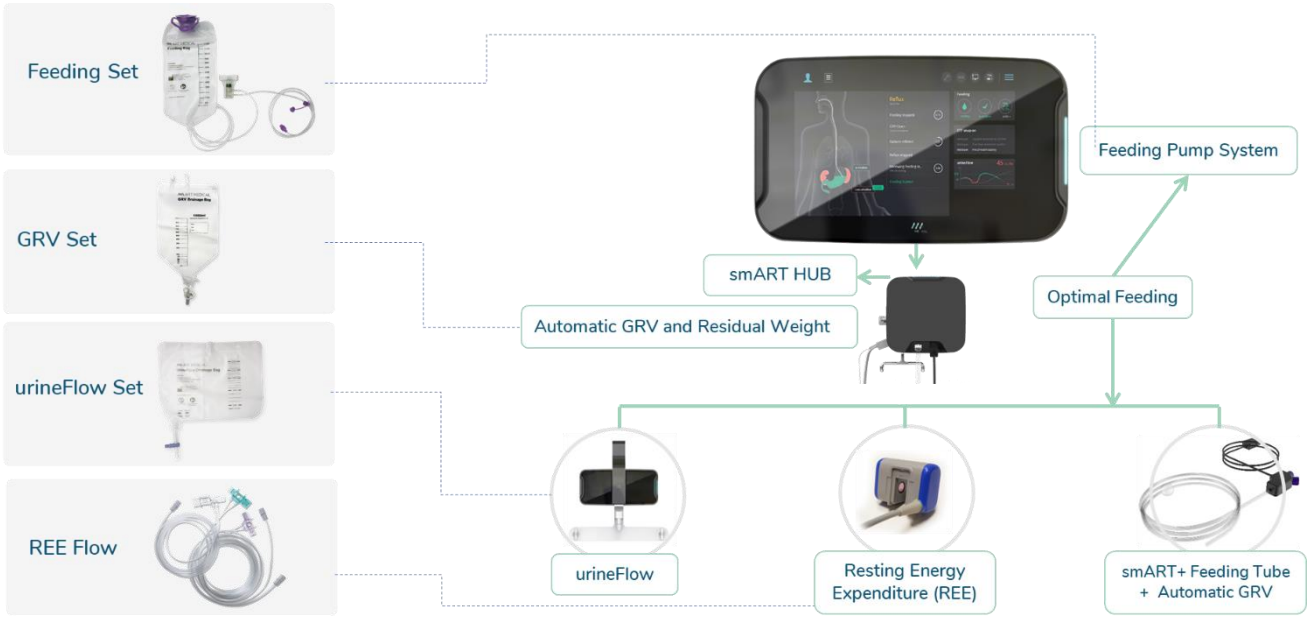
e) The Resting Energy Expenditure (REE) feature is comprised of a disposable flow rate meter and a reusable CO2 detector piece that are added between the patient's endotracheal tube and ventilation tubes. The REE has the capacity to continually measure the patient's energy

[8] Metheny. Effectiveness of an Aspiration Risk-Reduction Protocol. *Norma A*. **Nurs Res** (2010)

expenditure and deduce the patient's nutritional requirements, according to the following equation:

$$REE = \left[3.941\left(\frac{VCO2}{RQ}\right) + 1.11(VCO2)\right]1.44$$

f) The urineFlow disposable set connects to a urinary catheter, relaying urine through a tube and down to a viewing chamber into a collection bag. The viewing chamber is securely inserted into the urineFlow unit which is positioned horizontally off the patient's bed or on an adjacent IV pole. Drops falling through the chamber are captured by a camera mounted in the unit. The images are processed and the drop volumes are calculated and subsequently the patient's urine output rate is monitored. The urineFlow unit also includes a stabilizing mechanism to ensure that the unit is perpendicular to the ground at all times.



1.4. **Intended Use**

Europe: The smART+ System is a feeding optimization system that contains an anti-reflux mechanism, which uses the smART+ Feeding Tube with sensors to prevent gastric content from regurgitating to the esophagus and aspirating into the lungs. The system is intended to be used in healthcare setting.

USA: The smART+ System is a feeding optimization system that contains an anti-reflux mechanism, which uses the smART+ Feeding Tube with sensors and balloon to reduce gastric content from regurgitating to the esophagus. The system is intended to be used in healthcare setting.

1.5. **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.

1.6. Manufacturer and Manufacturing Information

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

1.7. 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

In addition to tube placement, the system allows to obtain REE measurements and calculates the optimized nutritional values required by the patient. Furthermore, the system optimizes feeding by compensating for any lost feeding time or discarded nutritional content that was discarded via the GRV.

1.8. Risk/Benefit Assessment

1.8.1. Known potential risks

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 smART+ disposables that come in any direct or indirect tissue contact.

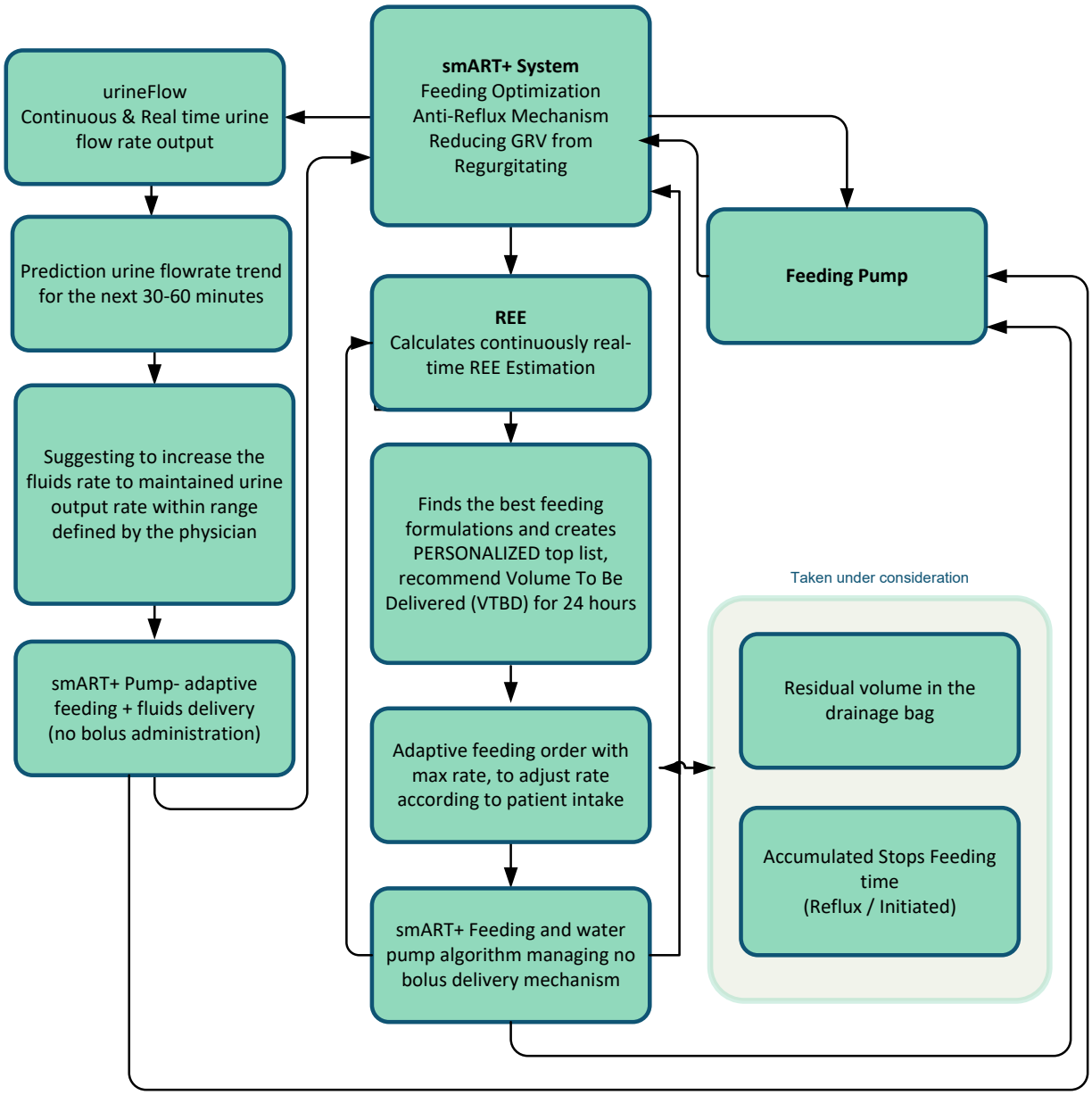
In addition, the results from previous studies supports the company's claim that the insertion, balloon inflation and feeding with the smART™ feeding tube are safe and tolerable. The results also show that the automatic GRV operates properly and efficiently, and the feeding tube device aids in the correct placement of the feeding tube into the patient.

ART Medical 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). The complete risk management document is available from the company upon request.

1.8.2. Known potential benefits

As explained above, the various components of the smART+ System must operate as a cohesive system in order to allow feeding optimization as demonstrated in the flowchart below. With validation of the smART+ 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 risks associated with reflux and aspiration.

In addition, the smART+ System is able to continuously measure the patients REE and minimize the risk of overfeeding. Therefore, by reducing overfeeding it not only achieves feeding optimization, but it also reduces the likelihood of reflux episodes due to overfeeding.



2. Objectives and Endpoints

2.1. **Primary Endpoint:**

Optimization of the delivery of nutrition by the smART+ System as compared to standard of care, by automatically calculating and administering enteral feeding better than standard of care (REE or Calorimeter).

Optimization is defined as the ability of the system to provide adequate nutrition (not overfeed or underfeed) when compared to treatment via standard of care.

Evaluation will be conducted based on an analysis and comparison of the following parameters (obtained through the hospital's electronic records for control group and smART+ records for the treated group):

- Patient caloric target set
- Volume of patient nutritional intake value versus actual patient need – this is calculated by assessing the actual nutrition delivered, discarded nutrition in the GRV bags as well as the unused quantity in discarded feed bottles (if applicable).

As part of optimization evaluation, feeding efficiency calculation ((Net nutrition delivered [ml])/ (VTBD [ml])) should be calculated for the days when the patient received enteral feeding that given under medical order, removed from the patient, or stopped feeding that was not renewed until the end of the study. Feeding efficiency should not be calculated for the days that patient has been discontinued from enteral feeding by a medical order.

2.2. **Secondary Endpoints:**

- Safety

  Safe use of the entire system will be assessed based on the occurrence of device related AE or SAE.

- Decrease in ICU length of stay.

  Measured from admission to ICU until the decision to discharge is ordered.

- Reduction of VAE According to the definition from the latest CDC.
- Decrease in ventilation days.

  Evaluated by the number of hours of etCO2 from the hospital electronic records

- Decrease in workload related to nurse GRV time.

  Patient GRV information obtained through the hospital's electronic records and the usability questionnaires, will be analyzed to determine (a) the estimated nursing time that was expended for GRV activities, and (b) the amounts of GRV removed from the patient.

- Convenience of use of the system and the user interface (by subjective staff questionnaire)

  Evaluated via questionnaires filled by physician users and nurse users participating in the study.

- Assessment of urine flow monitoring related to patient condition and usability

  Patient lab results obtained through the hospital's electronic records and the usability questionnaires, will be analyzed against smART+ system urine alerts, to determine if the alerts will be useful in diagnosis and usability satisfaction.

3. Study Design

3.1. Overall Design

The design of the study is as follows:

- Comparative: 2 groups. 100 participants per group
- Interim statistical analysis: planned after 50 patients
- Random: the randomization is controlled by APACHE score
- Multi-site: Israel, United States, Europe

3.2. End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA).
In addition, participant is considered to have completed the study if he/she is no longer required enteral feeding (due to feeding tube removal, medical order, or any other reason which feeding stopped and is not scheduled to be renewed within the 14 days of study duration).

4. Study Population

4.1. Inclusion Criteria

4.1.1. Males and females 18 years or older
4.1.2. Patients that have already been admitted to ICU (admitted to the ICU for no more than 48 hours before enrollment)
4.1.3. Expected to be ventilated at least 48 hours after enrollments.
4.1.4. Patient requires enteral feeding (by naso/oro-gastric feeding tube)

4.2. Exclusion Criteria

4.2.1. Pregnant women
4.2.2. Known anatomical anomalies of the nose, oral cavity, esophagus or the stomach that may prevent/hinder the ability to insert the feeding tube

4.3. Warnings

- Participants may not receive any kind of nutrition given NOT through the feeding tube (or one of its ports)
- MRI- the Feeding tube should be removed before performing the procedure.
- CPR- the feeding tube should NOT be disconnected from the Hub before performing the procedure.

4.4. Initial Screening

All patients already admitted into the ICU who require enteral feeding may be screened for potential enrollment into the study.

Any study procedure can be performed only following ICF signature process, as approved by the local IRB / EC, and in accordance with GCP.

The following information will be recorded in the study eCRF for each patient found eligible to participate in the study, as part of the initial screening:

- **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.
- **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.
- Inclusion/exclusion criteria

  The initial screening information will be recorded in the eCRF for all patients screened to participate in this study.

4.5. **Screen Failures**

Screen failures are defined as participants who were exanimated by the PI/Co-investigator as part of the initial screening process and were not subsequently entered to the study (e.g., patient found to be ineligible by the PI/Co-investigator, informed consent was not obtained, PI/Co investigator's discretion, etc.).

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes patient demographics, screen failure details, eligibility criteria, and any serious adverse event (SAE).

4.6. **Enrollment**

Patients may be included in the study only if:

- The assessment performed as part of the initial screening (part of the eCRF) is acceptable and patient was found appropriate to participate in the trial, according to the PI (or co-investigator) decision.
- Informed consent has been obtained.
- For women of childbearing age, a negative urine (or blood) pregnancy test.

5. Study Intervention

Following the initial screening procedure and after patient was found to be eligible to participate in the study, patients shall be divided into two study groups:
Group A- ICU patients receiving the investigational device (“Treated”)
Group B- Control group, receiving treatment according to local SOC.
The study intervention describes all study procedures and evaluations to be done as part of the study to support the determination of the primary and secondary objectives outlined in this protocol. Study source documents are defined as data collected from patient's medical chart (recorded in the hospital sources) as well as data collected by the smART+ System, as detailed in sections 5.2.8. and 5.3.5. below. In addition, video recording (as detailed in sections 5.2.1. and 5.3.1.) will be also used for later data analysis and serves as source data.

5.1. Divisions into Groups

After completion of the "initial screening" chapter in the study eCRF recruitment cycle, and after patient was found likely to participate in the trial, patients will randomly be divided into two groups.

Measures to minimize bias: randomization and blinding

Study participants will be randomly assigned to open-label study groups, in randomization ratio of 1:1.

In this current multicenter trial, the randomization procedures will be centrally organized. The ratio between treated and control groups should be balanced on each site.

In order to promote balanced allocation within the groups, the study randomization shall be stratified according to APACHE score measured at baseline.

To avoid possible bias in the selection and allocation of subjects and to ensure that the randomization is properly maintained throughout the trial, a computer randomization algorithm will be used for subject allocation to each group. The randomization algorithm will be part of the eCRF. Randomization will be implemented by the PI/Co-investigator after initial screening of the patient is completed (and before starting study procedures).

This will allow first of all the selection of suitable patients, and only then division into groups.

5.2. Group A- Interventional Device ("Treated")

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

5.2.1. Videotaping of subject- group A

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 behind/near the patient head, allowing recording of movements of the feeding tube and medical procedures for later comparison with the data logs recorded by the smART+ console. All recorded data must be attached to the patient files and serves as an integral part of the analyzable data for the study. The video recording is not binding and the PI or the sponsor may choose not to video a specific patient at certain times or at all.

5.2.2. Connecting the patient to the smART+ System

The patient should be connected up to all applicable modules of the smART+ as soon as possible after being enrolled in the study. Connection and use of the smART+ UrineFlow system will be as needed according to PI decision.

Detailed instructions of how to connect a patient to the system can be found in the smART+ User Manual and the accompanying Quick Guides.

5.2.3. Feeding insertion- group A

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 according to hospital procedures (such as abdominal /chest X-ray /other gold standard).

5.2.4. Vital signs- group A

Vital signs (e.g., temperature, pulse, respirations, blood pressure) should be noted within 10 minutes of feeding tube insertion.

5.2.5. REE measurement- group A

Once the patient has recovered from the process of inserting the feeding tube, a baseline REE measurement should be taken using the smART+ flow sensor and CO_2 sensor.

5.2.6. Feeding program- group A

Once the REE measurement is accomplished, personnel authorized by the hospital should program a suitable feeding program using the smART+ Console and in accordance with hospital procedure.

5.2.7. Ongoing use- group A

If system alerts of tube displacement during ongoing use, the need for tube reinsertion/repositioning should be evaluated and performed as needed.

If system alerts an increase in REE, the message should be evaluated by personnel authorized by the hospital, who should decide if to change the patient's feeding program.

5.2.8. Data recording- group A

The following information will be acquired from the patient's medical chart (recorded in the hospital sources) into the eCRF, for each patient

- Initial screening: as detailed in the study eCRF
- Feeding information: Food types, amounts, rate, water delivery, parenteral nutrition, TPN, other nutritional data
- Gastric residual volume: discard gastric residuals amount, GRV procedure times.
- Medications provided: as detailed in the study eCRF.
- Lab results: patient lab results, as detailed in the study eCRF, and obtained 24 hours prior the feeding tube insertion and during the study, should be recorded in the eCRF.
- Imaging: (X-ray, CT, and alike) performed during the study should be obtained and attached to the eCRF.
- Urine: amounts, rates, times, warnings
- ICU submission and discharge ordering times
- Breathing data reports starting from the ICU admission (FiO2, PEEP)
- Demographics

The following information will be recorded by the smART+ console (or accompanying recording equipment) and extracted directly by the sponsor:

- Urine monitoring: amounts, rates, times, warnings, trends (and all other data collected by the smART+ System).
- Feeding information: Food types, amounts, rate, fluids delivery (and all other data collected by the smART+ System).
- Gastric residual volume: GRV amounts and times
- Reflux and position data
- REE data
- Breathing data (collected by the smART+ System)
- All other data collected by the smART+ System.

5.2.9. Staff Questionnaires - group A

At the end of the study, staff will be required to complete a usability questionnaire assessing the convenience of using the system and the user interface. Two different questionnaires will be used for either physician users and nurse users participating in the study. The questionnaires will include a variety of questions such as YES/NO, open-ended and scoring-based questions.

5.3. **Group B- Control Group**

5.3.1. Nutrition camera - group B

Local site procedure for changing feeding bottle/bag should be followed as needed and according to hospital procedures. An additional camera (Nutrition camera) will be added, pointed directly at the feeding bottle/bag area and not on the patient.

The Nutrition camera will record a real time video and automatically save it in storage device (such as PC). This camera captures the amount of feeding discarded that was not used for patient feeding. It will allow later data analyzation to quantify the amount of feeding discarded by using the grid lines marked on the feeding bag's/bottle's exterior. In order to ensure the effectiveness of the Nutrition camera, it will bear an instruction such as Ensure camera points at feeding bottle/bag.

5.3.2. REE or calorimeter measurement- group B

Once the patient is enrolled in the study a baseline REE or calorimeter measurement (according to gold standard in the department) should be taken using available department equipment.

5.3.3. Feeding program - group B

Once the REE \ calorimeter measurement \ other method to determined caloric target is obtained, personnel authorized by the hospital should administer a suitable feeding program per hospital standard of care (i.e., hospital's usual available feeding tubes, feeding pumps, gravity feeding, etc.).

5.3.4. On-going treatment- group B

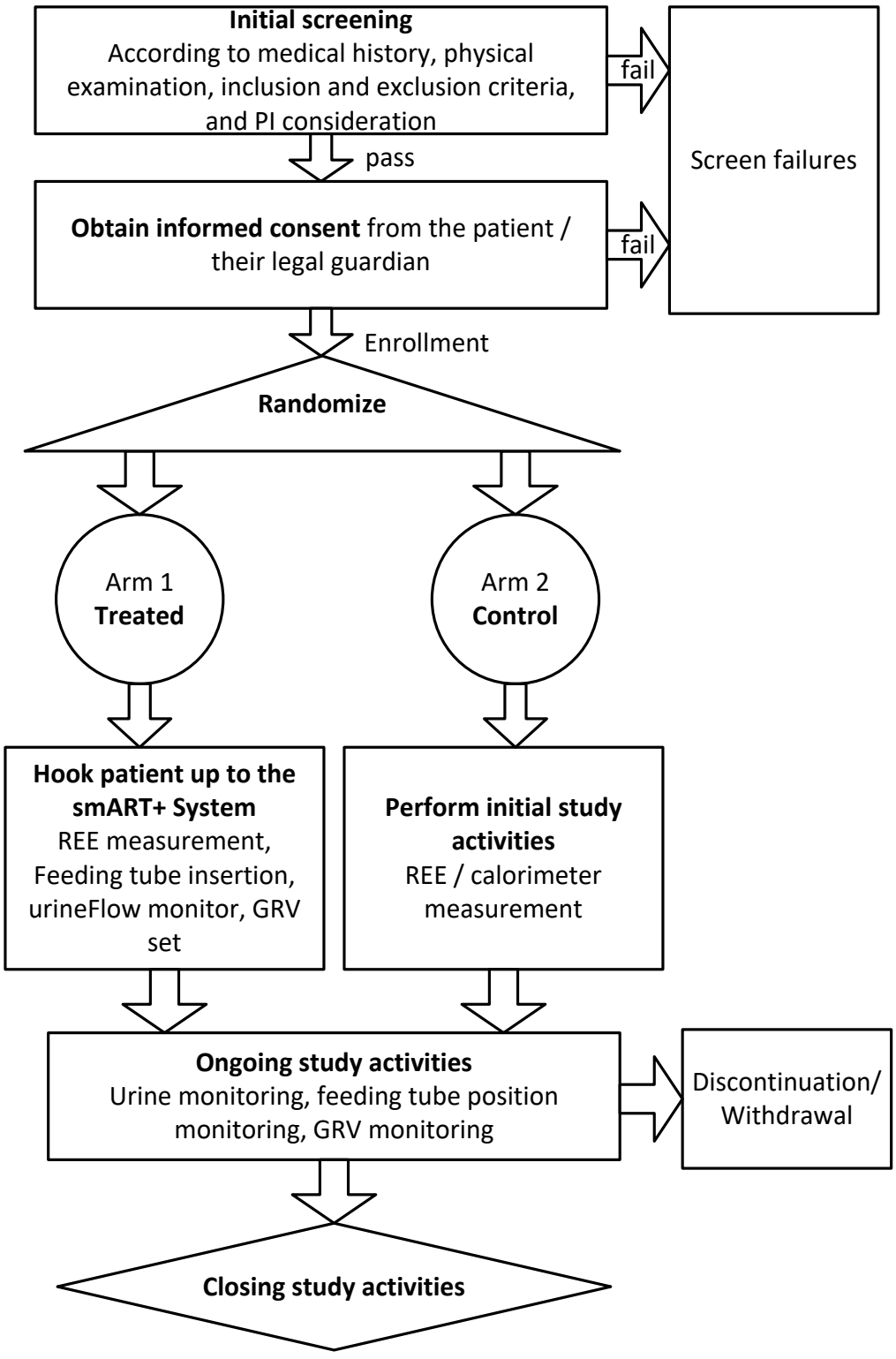
Patients in the control group should be treated in accordance with standard hospital procedures per usual hospital/physician determined treatment plan.

5.3.5. Data recording- group B

The following information will be acquired from the patient's medical chart (recorded in the hospital sources) for each patient:

- Initial screening: as detailed in the study eCRF
- Feeding information: Food types, amounts, rate, water delivery, parenteral nutrition, TPN, Indirect calorimeter and other nutritional data.
- Gastric residual volume: discard gastric residuals amount, GRV procedure times.
- Medications provided: as detailed in the study eCRF.
- Lab results: all patient lab results ordered during the study as well as all available lab results obtained 24 hours prior to study enrollment and added to the eCRF.
- Imaging: patient imaging (X-rays, CT, and alike) performed during the study should be obtained and added to the eCRF.
- Urine monitoring: amounts, rates, times, warnings and all data related to urinary output and diagnosis, and found in the hospital source.
- ICU submission and discharge ordering times
- Breathing data reports starting from the ICU admission (FiO2, PEEP)
- Demographics

5.4. **Study Flowchart**



5.5. **Schedule of Activities (SoA)**

Procedures	Screening/ enrollment	Medical Device Placement	Ongoing use	Termination
Day	1	1(T)	Up to 14	1 up to 14
Informed Consent	T+C			
Eligibility Criteria	T+C			
Physical Exam	T+C			
Pregnancy test (if applicable)	T+C			
Videotaping		T+C	T+C	
Vital Signs		T+C	T+C	T+C
REE or calorimeter/spirometer measurement		T+C	T as needed and according to procedures	
Lab Data			T+C	T*+C*
Medical Device Administration		T	T	
GRV Measurements			T+C as needed and according to procedures	
Urine monitoring			T as needed and according to procedures	
Adverse Events	T+C	T+C	T+C	T+C
Concomitant Medication		T+C	T+C	T+C
Information regarding nutritional supplement administration		T+C	T+C	

T – group A – "Treated"
C – group B – "Control"
* - For T only – obtained retroactively 24 hours prior the feeding tube insertion and during the ongoing study

6. Preparation/Handling/Storage/Accountability

6.1. Acquisition and accountability

All disposables and capital equipment will be provided to the investigator directly by the sponsor.

The site will store the capital equipment throughout the entire period of the trial.

The disposables will be delivered to the sites (in quantities or in individuals) according to the enrollment rate. The sponsor will ensure that the site has a sufficient amount of equipment (capital

and disposable) for replacement of damaged equipment/parallel experiments/additional participants.

Device Receipt logs will be updated accordingly.

6.2. Used/unused devices

Used disposable devices will be discarded after opening/ use according to hospital procedures. Accountability logs will be updated accordingly.

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

6.3. Packaging and labeling

smART+ System information can be obtained from the:

- Investigator brochure (IB)
- Package or device labeling/instruction for use (IFU)
- Device quick guides
- User manual

7. Study Discontinuation and Participant Discontinuation/Withdrawal

7.1. Participant Discontinuation/Withdrawal from The Study

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 discontinuation/withdrawal:

- The insertion of the feeding tube has failed after 3 attempts in each nostril
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

In the event a subject discontinuation/withdraws from the study the following procedures will be observed:

- The reasons for any subject discontinuation/withdrawal will be recorded on the study completion form of the eCRF.
- The investigator will inform the sponsor 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.

Subjects who signed the informed consent form and are randomized but do not received the study intervention are considered screen failures and may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study may also be replaced.

In addition, this study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause.

Circumstances that may warrant termination or suspension include according to the PI decision, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

7.2. **Medical condition resulted in the decision to deliver "Comfort-oriented care"**

If during the study patient's medical condition changed and the decision/preferences is NOT to receive aggressive, life-sustaining treatments but to delivered comfort-oriented care (or equivalent according to hospital policy and PI confirmation), subject should be terminated from the study.

If in this case the smART+ feeding tube cannot be removed (since a tube must be kept for drainage purposes and a new tube should not be inserted), the feeding tube can continue to be used for drainage / other treatment purposes under the comfort-oriented care.

Although in this case the smART+ feeding tube can be left inside the patient, it must be disconnected from the smART+ device (and all other smART+ components).

7.3. **Follow-Up**

No follow-up will be conducted for this study. AE and SAE collection is to be conducted up until the moment the subject study participation is terminated. AEs and SAEs occurring after study termination are not to be collected or reported for the purpose of this study.

7.4. **Adverse Events and Serious Adverse Events**

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during filling of the eCRF, treatments/other medical procedures or upon review by a study monitor.

7.4.1.Adverse events (AE)

AE DEFINITION

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

NOTE 1- This includes any event that is a result of a use error or intentional misuse.

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.

AE CLASSIFICATION AND REPORTING

Group A- Interventional Device

All AEs will be recorded on the adverse events page of the eCRF. AEs will be recorded after the subject (or delegate) has signed the informed consent and throughout the study. Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. AE reporting and documentation will be discontinued, at the end of the study, immediately after feeding tube removal.

Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring during the study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Severity and relationship to study device will be assigned by the investigator as described below.

All adverse events will be graded for severity as follows:

- Mild: Events, sign or symptom, usually transient, requiring minimal or no special treatment and generally not interfering with participant's usual activities.
- Moderate: Events, sign or symptom, which may be ameliorated by simple therapeutic measures; yet, may interfere with usual activity.
- Severe: Events, sign or symptom that are intense or debilitating and that interfere with usual activities. Recovery is usually aided by therapeutic measures.

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **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.

Group B- Control Group

AEs recorded for group B should include only related or could affect (according to PI decision) the patient's medical condition that related to urine, feeding, GRV and REE.

7.4.2.Serious Adverse Events (SAE)

SAE DEFINITION

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.

SAE REPORTING

Due to the complex clinical status of the patients a very large number of AEs and SAEs occur; therefore, ***only device related SAEs will be reported to the IRB / local ethic committee***.

This is in line with information provided in FDA guidance document “Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs - Improving Human Subject Protection”. Per the guidance and the IDE regulation, reportable events to the IRB are: “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 investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.”

The guidance further states: “Sponsors can assess the implications and significance of AE reports promptly and are required to report serious, unexpected events associated with the use of a drug or device, including analyses of such events, to investigators and to FDA. In addition, sponsors are required to report analyses of unexpected adverse device experiences to IRBs.”

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as

possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

Accompanying documentation, such as copies of hospital case reports, autopsy report, and other documents when applicable, should be sent to the sponsor as soon as they are available.

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

7.4.3. Expected / anticipated adverse events

Expected/anticipated adverse events are AEs that are known to occur for the study intervention being studied and should be collected and recorded in the study eCRF (as other AEs).

<u>Anticipated adverse events associated with the insertion and presence of feeding tubes include:</u>

- 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 feeding tube.
- Nausea and vomiting
- Pneumothorax

Anticipated adverse events associated with feeding are:

- Abdominal discomfort and pain
- Abdominal bloating
- Diarrhea

The study PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Expected/anticipated adverse events will be reported in the study eCRF and marked as "Expected/anticipated adverse events".

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 MEDICAL 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.
The investigational site will provide to the monitor direct access to the trial related source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

9. Statistical Considerations

9.1 Sample size consideration

Approximately 200 subjects will be enrolled for the complete multi-center comparative study (100 per group). An interim analysis will be performed after 100 subjects (50 in each group) are enrolled on the primary endpoint.

1- **Based on the primary endpoint at interim analysis (feeding efficiency):**

Sample size rationale:

The rationale for sample size calculation is based on a difference in feeding efficiency between the tested group (with smART+ System) and the current standard practice (group B).

Sample size justification:

The comparison between groups of food consumption estimations is reflected by Effect size, calculated as the difference between the groups normalized by the common standard deviation.
The calculation uses the following formulation: (Estimation in the tested group - Estimation in control group)/Common standard deviation [Error! Bookmark not defined.,Error! Bookmark not defined.].

A sample size of 50 in each group will have 90% power to detect an **effect size of 0.70** using a two-group t-test with a 0.025 two-sided significance level. [1, 2]
A significance of 0.025 was used instead of the usual 0.05 (alpha adjustment) due to the increase in the chance of making a Type 1 error following two subsequent analysis.

2- Based on the secondary endpoints at end of study:

2.1 Ventilation days:

Sample size rationale:

The rationale for sample size calculation is based on a difference in Ventilation days between the tested group (with smART+ System) and the current standard practice (group B).

Sample size justification:
The comparison between groups in ventilation days is reflected by Effect size.
A sample size of 100 in each group will have 90% power to detect an **effect size of 0.46** using a two group t-test with a 0.05 two-sided significance level. [1, 2]

2.2 Ventilation Associated Events:

Sample size rationale:
The rationale for sample size calculation is based on a difference in the proportion of subjects with Ventilation-Associated Events between the tested group (with smART+ System) and the current standard practice (group B) of 20%.

Sample size justification:
A two group continuity corrected c^2 test with a 0.05 two-sided significance level will have 90% power to detect the difference between a Group 1 proportion, p_1, and a Group 2 proportion, p_2 (**odds ratio of 2.70**) when the sample size in each group is 100.[3]

2.3 Length of stay:

Sample size rationale:
The rationale for sample size calculation is based on a difference in length of stay between the tested group (with smART+ System) and the current standard practice (group B).

Sample size justification:
The comparison between groups in ventilation days is reflected by Effect size.
A sample size of 100 in each group will have 90% power to detect an **effect size of 0.46** using a two group t-test with a 0.05 two-sided significance level. [1, 2]

References:
1. Dixon, W.J., Massey, F.J. **Introduction to Statistical Analysis. 4th Edition** McGraw-Hill (1983)
2. O'Brien, R.G., Muller, K.E. **Applied Analysis of Variance in Behavioral Science** Marcel Dekker, New York (1983) pp. 297-344
3. Fleiss, J.L., Tytun, A., Ury, S.H.K. "A simple approximation for calculating sample sizes for comparing independent proportions" *Biometrics* 36(1980) pp. 343-346

9.2 Endpoints analysis:

9.2.1 General:

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics.

For categorical variables summary tables will be provided giving sample size, absolute and relative frequency and 95% CI (Confidence Interval) for proportions by study arm.
For continuous variables summary tables will be provided giving sample size, arithmetic mean, standard deviation, coefficient of variation (CV%), median, minimum and maximum and 95% CI (Confidence Interval) for means of variables by study arm.
All tests will be two-tailed, and a p value of 5% or less will be considered statistically significant.
The data will be analyzed using the SAS ® version 9.4 (SAS Institute, Cary North Carolina).

9.2.2 Primary endpoint:

The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference in feeding efficiency between the study groups.

9.2.3 Secondary endpoints:

- The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference in number of ventilation days (Evaluated by the number of hours of etCO2 from the hospital electronic records) between the study groups.
- The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference in the estimated nursing time that was expended for GRV activities, and the amounts of GRV removed from the patient between the study groups.
- Convenience of use of the system and the user interface scores (by subjective staff questionnaire) will be summarized in an appropriate table by study group
- The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference in the assessment of urine flow monitoring related to patient condition and usability between the study groups.
- The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference in ICU length of stay (measured from admission to ICU until the decision to discharge is ordered) between the study groups.
- Chi-square test or Fisher's Exact test (as is appropriate) will be applied for testing the statistical significance of the difference in percent of subjects experiencing Ventilation associated events between the study groups.

9.2.5 Safety:

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, most updated version) terminology and presented in tables by System Organ Class (SOC) and Preferred Term (PT).

AE data will be listed individually and summarized by SOC and by PT within a system organ class for each study group.
Frequency of TEAEs (Treatment-Emergent Adverse Events) and device-related adverse events will be summarized in tables by SOC, PT and study group and by seriousness.
Chi-square test or Fisher's Exact test (as is appropriate) will be applied for testing the statistical significance of the difference in percent of subjects experienced any AE, drug-related AE and SAE between the study groups.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.

10. Regulatory, Ethical, and Study Oversight Considerations

10.1. Informed Consent Process and Documentation

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.

Informed consent process is initiated prior to the individual’s participation in the study and continues throughout the individual’s study participation. Consent forms will be Institutional Review Board (IRB)-approved and the patient/patient representative will be asked to read and review the document prior to starting intervention. The investigator will explain the research study to the patient/patient representative and answer any questions that may arise. A verbal explanation will be provided in terms suited to the patient/patient representative comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. patient/patient representative will have the opportunity to carefully review the written consent form and ask questions prior to signing. The patient/patient representative should have the opportunity to discuss the study with their family or think about it prior to agreeing to participate. The participant (or a legal representative on their behalf) will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the patient/patient representative for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.1. Confidentiality and privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover all the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict

confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible. As previously mentioned, during the study, a video recording of the treated patient (group A) is obtained. The camera will be placed behind/near the patients' head, allowing recording of movements of the feeding tube and medical procedures, without revealing the identity of the patient.

As mention above, in the control group (group B), a Nutrition camera will be placed pointed at feeding bottle/bag area, without revealing the identity of the patient.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored safely by the sponsor. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the research staff will be secured and password protected.

10.1.2. Data collection and management responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data from each subject will be recorded as part of the routine data collection & recording, in the hospital source documents or (but not limited to) in the patient's medical charts (as accepted in the department). Later, the data will be transferred by the investigator to the eCRFs supplied by the sponsor. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Quality check for errors and omissions will be performed to ensure the accuracy of the entered data.

The eCRF should be completed in full, i.e., no fields should be left blank once the subject has completed the study. The investigator must review the eCRFs for completeness and accuracy and must sign/date the forms where indicated. The investigator shall retain

originals of eCRFs, subject consent forms, and study data as permanent records for the period indicated under "STUDY RECORD RETENTION" below.

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

10.1.3. Protocol deviations

Noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Any deviations from the study protocol should be reported to the sponsor and documented on study deviation forms. Further details about the handling of protocol deviations will be included in the study SOP/MOP.

10.1.4. Publication and data sharing policy

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

10.1.5. Conflict of interest policy

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

11. Resources:

[1] Code of Federal Regulations (CFR)

- 21 CFR Part 11: Electronic Records, Electronic Signatures
- 21 CFR Part 50: Protection of Human Subjects
- 21 CFR Part 54: Financial Disclosure by Clinical Investigators
- 21 CFR Part 56: Institutional Review Boards
- 21 CFR Part 812: Investigational Device Exemptions
- 42 CFR Part 11: Clinical Trial Registration and Results Information Submission

[2] Food and Drug Administration (FDA)

- Compliance Actions and Activities
- FDA Regulations Relating to Good Clinical Practice and Clinical Trials
- Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs – Improving Human Subject Protection
- Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees
- Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance
- Guidance for Industry: Electronic Source Data in Clinical Investigations
- Guidance for Industry: Multiple Endpoints in Clinical Trials
- Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring

- Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications
- Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Standardized Study Data
- Guidance for Industry: Safety Assessment for IND Safety Reporting

[3] Department of Health and Human Services (HHS)
- The HIPAA Privacy Rule
- HIPAA Privacy Rule: Information for Researchers

[4] ISO 14155:2011 - Clinical Investigation of Medical Devices for Human Subjects -- Good Clinical Practice

[5] Israel's Health Department procedure for the conduct of clinical trials: https://www.health.gov.il/hozer/DR_14.pdf

12. References

Footnotes in the relevant places along the document.