A FEASIBILITY STUDY TO EVALUATE THE CLINICAL SAFETY OF NUTRISEAL™ NASOENTERAL FEEDING TUBE PLACEMENT USING THE NUTRISEAL™ NUTRIPLACE™ SYSTEM IN PATIENTS

Protocol Number: NUTRI-001

Principal Investigator: Dr. May Olayan

Sponsor: Nutriseal L.P.

Version Number: 1.1

February, 4 2018

Summary of Changes from Previous Version:

#	Section	Previous wording (Ver. 1.0)	New wording (Ver. 1.1)	Rationale for revision
1.	1.1- Number of Subjects and Sites (Synopsis)	Fifty (50) subjects will be enrolled at a single center by at least five operators. Prior to participating in this trial each operator will place a Nutriseal nasoenteral feeding tubes in a run-in patient to provide training on the use of the NUTRIPLACE System.	Fifty (50) subjects will complete the Procedure Visit (NasoEnteral Tube placement procedure, section 1.3) at a single center by at least five operators. This number (50 subjects) does not include screen failures. Prior to participating in this trial each operator will place a Nutriseal nasoenteral feeding tubes in a run-in patient to provide training on the use of the NUTRIPLACE System.	To clarify that the 50 enrolled subjects will complete the Procedure Visit
2.	1.1 Sample size consideratio ns (Synopsis)	There is no statistically based sample size for this study which is being conducted to obtain confirmatory evidence to support the safety of using the NUTRIPLACE System as an adjunct to current placement practices for nasoenteral feeding tubes. Fifty (50) patients will provide evidence that the NET tube guidance system does not present new or different safety issues as compared to the predicate (confirmatory study).	There is no statistically based sample size for this study which is being conducted to obtain confirmatory evidence to support the safety of using the NUTRIPLACE System as an adjunct to current placement practices for nasoenteral feeding tubes. Fifty (50) patients completing the Procedure Visit (NasoEnteral Tube placement procedure) will provide evidence that the NET tube guidance system does not present new or different safety issues as compared to the predicate (confirmatory study). If less than 45 patients will complete the Follow-up Visit (confirmation of tube tip anatomical location, section 1.3), an enrollment of another 5 patients will be considered.	To clarify sample size population
3.	1.1 Exclusion Criteria (Synopsis) 5.2 Exclusion Criteria (Study population)		Upper airway obstruction	Upper airway obstruction was added as an exclusion criteria - Such obstructions can prevent insertion of feeding tube

4.	1.1 Exclusion Criteria (Synopsis) 5.2 Exclusion Criteria (Study population)	Gastrointestinal surgeries		Gastrointestinal surgeries was omitted as an exclusion criteria- Not required as standard patient population may well have undergone Gastrointestinal surgery. Moreover, participation in the study of a subject who underwent a Gastrointestinal surgery should be per Investigator's discretion as there is other exclusion criteria: "Patients must not have a significant concomitant illness that would adversely affect their participation in the study".
5.	1.1 Exclusion Criteria (Synopsis) 5.2 Exclusion Criteria (Study population)	Failed tube placement in the last seven days		Failed tube placement in the last seven days was omitted as an exclusion criteria- Redundant as Chest X-Ray demonstrates if there is presence of any lung damage caused by a previously inserted feeding tube
6.	5.4 Screen Failure	Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. 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)	Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study and do not complete the Procedure Visit. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of	To clarify the definition of screen failures

		publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).	Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).	
7.	9.2 Sample Size Determination	This feasibility trial will include fifty (50) patients and five operators. Each operator must complete training on one run-in subject prior to participating in this study.	This feasibility trial will include fifty (50) patients completing the Procedure Visit (NasoEnteral Tube placement) and five operators. Each operator must complete training on one run-in subject prior to participating in this study. Patients or patients' LAR who chose not to participate after informed consent but prior to procedure and patients who because of system malfunction or because of undiscovered or unreported physical reasons (e.g. deteriorating health, anatomical anomalies, mechanical obstruction, etc.) cannot complete the Procedure Visit (NasoEnteral Tube placement) will be considered Screen Failures, not be considered in the total patient count, but will be reported in the ITT dataset as defined below. If less than 45 patients will complete the Follow-up Visit (confirmation of tube tip anatomical location), an enrollment of another 5 patients will be considered.	To clarify sample size population

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STATEMENT OF COMPLIANCE

Investigator Signature Page

Study Title:	A Feasibility Study to Evaluate the Clinical Safety of Nutriseal™ Nasoenteral Feeding Tube Placement using the Nutriseal™ NUTRIPLACE™ System in Patients (NUTRI-001)
Investigational Devices:	NUTRIPLACE System
	Nutriseal™ NasoEnteral Tube
Protocol Version:	Version 1.1
Protocol Date:	February, 4 2018
Sponsor:	Nutriseal L.P.

Prior to participation in the clinical study (Protocol Number: NUTRI-001), as the Principal Investigator, I understand that I must obtain written approval from my Institutional Review Board (IRB). This approval must include my name, and I must send a copy to Nutriseal (the COMPANY) or designee along with the IRB-approved Informed Consent Form (ICF) prior to study enrollment at my study site.

As the Principal Investigator, I must also:

1. Conduct the study in accordance with the study protocol, the signed Clinical Investigation Agreement, HIPAA requirements, IRB requirements and applicable FDA regulations (21 CFR Part 812, 50, 54 and 56) and ensure all study personnel are appropriately trained.
2. Provide a copy of my curriculum vitae which includes my relevant professional experience including the dates, location, extent, and type of experience.
3. Supervise all testing of the investigational device in this study.
4. Ensure that the study has not commenced until IRB approval has been obtained.
5. Immediately inform the COMPANY in writing if I become debarred from conducting clinical studies by FDA, or any professional organization (e.g., loss of medical license).
6. Ensure that written informed consent is obtained from each patient prior to any study activities using the most recent IRB-approved Patient ICF.
7. Provide all required data and reports and agree to source document verification of study data with patients' medical records.
8. Allow the COMPANY personnel or its designees, as well as FDA representatives, to inspect and copy documents pertaining to this investigation.
9. Provide sufficient and accurate financial disclosure information and update information if any relevant changes occur during the investigation and for one year following the completion of the study.
10. If involved in research that was terminated, I will provide an explanation in writing of the circumstances that led to the termination of the research.

I have read and understand the contents of the Origin study protocol and agree to abide by the requirements set forth in this document.

Dr. May Olayan_____ Cleveland Clinic Foundation_____

Investigator Name Investigative Site Name

_____ _____

Investigator Signature Date

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

STUDY TITLE	A Feasibilty Study to Evaluate the Clinical Safety of Nutriseal™ Nasoenteral Feeding Tube Placement using the Nutriseal™ NUTRIPLACE System in Patients.
PROTOCOL NUMBER	NUTRI-001
DEVICE DESCRIPTION	The Nutriseal™ NUTRIPLACE™ System is designed to aid qualified operators in the placement of the Nutriseal™ NasoEnteral Tube™ of 10 Fr to 12 Fr into the stomach or small intestine of patients requiring enteral feeding. The NUTRIPLACE System is intended as an adjunct to current placement practices for assisting clinical practitioners who place feeding tubes in adult patients. The Nutriseal™ NasoEnteral Tube has been specifically designed for use with the NUTRIPLACE™ System and is intended for placement in the stomach or small intestine. It is intended for use in adult patients who require intermittent or continuous feedings via the nasogastric or nasoenteric route.
STUDY OBJECTIVES	The objective of this study is to assess the safety of the NUTRIPLACE System as an adjunct to current practices for placement of nasoenteral feeding tubes.
STUDY DESIGN	The study is a prospective, single center, non-randomized clinical trial in patients that require placement of a nasoenteral feeding tube as a result of their current medical condition.
NUMBER OF SUBJECTS AND SITES	Fifty (50) subjects will complete the Procedure Visit (NasoEnteral Tube placement procedure, section 1.3) at a single center by at least five operators. This number (50 subjects) does not include screen failures. Prior to participating in this trial each operator will place a Nutriseal nasoenteral feeding tubes in a run-in patient to provide training on the use of the NUTRIPLACE System.
DURATION OF PARTICIPATION/STUDY	Each patient's individual participation will last approximately 20-48 hours. It is expected the entire study will take approximately two (2) months to complete.
STUDY ENDPOINTS	<u>Primary Endpoint</u>: Procedure success: Nasoenteral tube (NET) can be placed in the correct anatomical position without occurrence of guidance-related adverse events. <u>Additional Assessments:</u>

	Procedure Metrics: Number of placement attempts required Safety: Adverse Events
SAMPLE SIZE CONSIDERATIONS	There is no statistically based sample size for this study which is being conducted to obtain confirmatory evidence to support the safety of using the NUTRIPLACE System as an adjunct to current placement practices for nasoenteral feeding tubes. Fifty (50) patients completing the Procedure Visit (NasoEnteral Tube placement procedure) will provide evidence that the NET tube guidance system does not present new or different safety issues as compared to the predicate (confirmatory study). If less than 45 patients will complete the Follow-up Visit (confirmation of tube tip anatomical location, section 1.3), an enrollment of another 5 patients will be considered.
SCHEDULED VISITS	This study is an acute safety assessment of the NUTRIPLACE System covering the guidance functionality of the System. <u>Screening</u> The screening visit will occur at time zero and will assess eligibility for the study and obtain informed consent. <u>Procedure</u> The study procedure may occur within two days of screening. Informed consent will be affirmed and the patient will be considered enrolled. <u>Final Follow Up</u> The final follow-up visit will occur 20-48 hours following the procedure.
INCLUSION CRITERIA	• Patients must be ≥21 years of age • Patients must require placement of a nasoenteral feeding tube • Patients have an endotracheal tube, OR ○ Do not have an endotracheal tube but are sedated and/or classified as obtunded[1] at the time of placement • Patients or legal authorized representative must be able to understand and adhere to all protocol procedures and be willing and able to provide written informed consent[2]

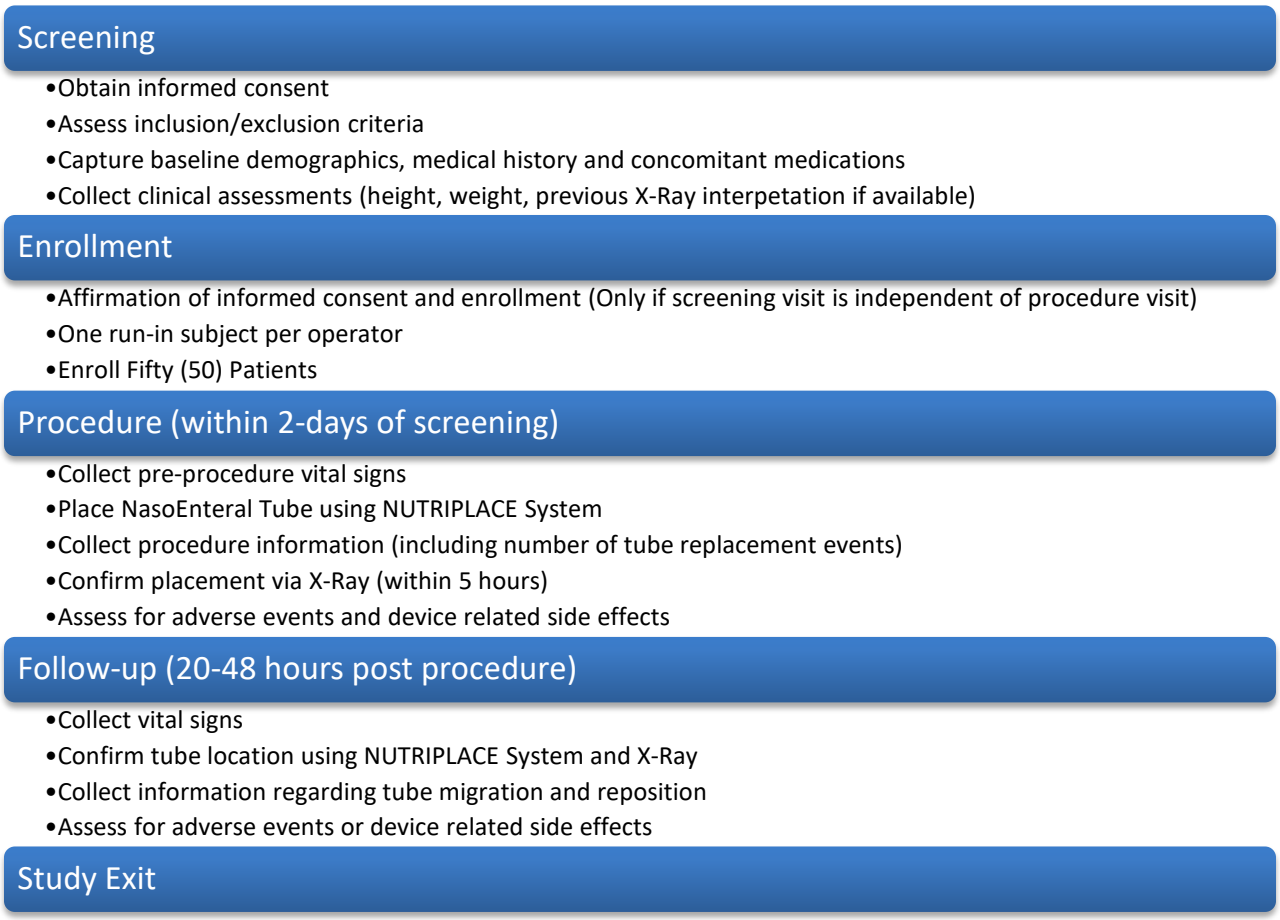
EXCLUSION CRITERIA	• Patients must not have a history of:
	  ○ Esophageal varices or ulcers
	  ○ Upper airway obstruction
	  ○ Upper GI stenosis or obstruction

[1] Obtundation level evaluation is based on Glasgow-Coma scale with a score of between 9 and 12. Sedation level is based on Richmond Agitation-Sedation Scale (RASS) score of -2 or less.
[2] Consent may be provided by patient's legal authorized representative.

	○ Trauma involving sinuses, nares face or neck that would prevent NG tube insertion ○ Deformities of the sinus cavities and/or skull base ○ Esophageal cancer or neoplasm • Patients must not have a significant concomitant illness that would adversely affect their participation in the study • Female patients who are pregnant or lactating
STATISTICAL ANALYSIS	All data will be reported using summary statistics.
OTHER CONSIDERATIONS	No core lab will be charted for this study; thus, judgements regarding placement will be based on the investigator's assessment of X-Ray images. Assessments of relatedness of any noted adverse events to the study device will be adjudicated by a Clinical Events Committee (CEC). No DSMB will be chartered for this study based on the well-understood safety profile.
US REGULATORY STATUS	The NUTRIPLACE System is considered a non-significant risk investigational device in the United States.

1.2 SCHEMA

Figure 1: Study Flow Chart



1.3 SCHEDULE OF ACTIVITIES (SOA)

The study schedule for this evaluation is presented below in **Table 1.**

Table 1: Study Schedule

Procedures, Evaluations and Tests	**Study Visits**		
	Screening	**Procedure (Within 2 days of Screening Visit)**	**Follow-up (20-48 hours after Procedure Visit)**
Informed Consent	X	X[3]	
Inclusion/Exclusion Criteria	X		
Demographics	X		
Medical History (Acute and Past)	X		
Concomitant Medications[4]	X		
Examinations Targeted Physical Exam Vital Signs	X	 X	 X
Nutriseal™ nasoenteral tube Placement		X	
Confirm Anatomical Location NUTRIPLACE System Abdominal and/ or thoracic X-ray[5]		 X[6]	 X X
Adverse Events		X	X

[3] Affirmation of informed consent is only required if procedure visit is independent of screening visit.
[4] Limited to sedatives/any medication with sedative effect, anticoagulants and prokinetic agents.
[5] Additional X-Rays may be taken if clinically indicated.
[6] Within five hours of placement.

2 INTRODUCTION

2.1 STUDY RATIONALE

This clinical study is designed to affirm the utility of the NUTRIPLACE System during placement of the Nutriseal nasoenteral feeding tubes.

2.2 BACKGROUND

Enteral nutrition is the preferred route for the provision of nutritional support in most critical ill patients with functional gastrointestinal tract. The nasoenteric tube (NET) are easily placed at the bedside. Patients that most commonly require a NET are in the surgical, intensive care, neonatal and pediatric settings[1,2]. Enteral tube feeding is thought to preserve the integrity of the gut mucosa, and to reduce infectious complications. Achieving early enteral nutrition (EN) in critically ill patients is associated with fewer major complications, reduced mortality and length of hospital stay, and significant cost savings[3,4,5,6,7].

It is estimated that approximately 1.2 million feeding tubes are placed blindly each year in the United States alone[2,8,9,10,11]. Despite the obvious advantages of the enteral tube feeding, inadvertent placement of NET into the airway is relatively common and can result in significant pulmonary injury including pneumothorax and pneumonia. Airway misplacement occurs in 1.2–4 % of blind NET insertions, with 0.2 to 1.2% of all the feeding tube placements cause pulmonary complications to patients[3,12,13,14,15,9].

The gold standard for detecting inadvertent placement of a feeding tube in the lungs is radiography. However, because of its cost, possible delay of feedings while waiting for radiography, and risk for radiation exposure, clinicians continue to seek for alternative methods to confirm correct placement[3,16].

All the above mentioned, emphasizes the fact that safe and effective delivery of nasoenteral tube feedings requires assurance that the feeding tube tip is in a proper position[17].

The NUTRIPLACE System is an electromagnetic tracking system which tracks the path of the feeding tube during placement. The System utilizes an ElectroMagnetic (EM) sensor in the NET's distal tip and a field generator as well as plate sensor (patient angle) and reference sensor (provides horizontal scaling of the body contour of the patient) and a Stylus which marks two anatomical landmarks (Xiphoid Process and Suprasternal Notch).

The benefit of the system when NET is misdirected into the pulmonary system is a real-time visual tracing, which may prompt users to withdraw the tube and reinsert it.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risks associated with the placement and use of nasoenteral tubes include the following:

- Placement in the lungs resulting in:
  - pneumothorax
  - pneumonia and sepsis
- Irritation and coughing during placement
- Damage to nasal ciliary epithelium leading to infection and/or sinusitis following long-term presence of an nasoenteral tube
- Perforation of the esophagus in patients with esophageal varicies, ulcers, or history of cancer or neoplasms
- Perforation of the base of the skull in patients with deformities of the skull base and/or sinus cavity
- Reflux of stomach contents into the esophagus leading to aspiration
- Parotitis
- Minor bleeding during tube placement

2.3.2 KNOWN POTENTIAL BENEFITS

Potential benefits provided by the NUTRIPLACE System include improved placement accuracy for enteral feeding tubes, shorten time to confirm tube position, earlier enteral nutrition, immediate detection of tube misplacement and therefore reduced likelihood of incorrect tube placement, feeding into lungs and pneumothorax. The use of enteral feeding is intended for situations where such means are necessary to potentially save the patient's life.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Taking into consideration all risks identified during analysis, and the benefits the NUTRIPLACE System provides to the patient, it has been determined to be an acceptable residual risk when weighed against the intended performance benefits.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The objective of this study is to assess the safety of the NUTRIPLACE System as an adjunct to current practices for placement of nasoenteral feeding tubes.	Procedure success: NET tube can be placed in the correct anatomical position without occurrence of guidance-related adverse events.	This endpoint will support the performance of the NUTRIPLACE System guidance.
Secondary		
There are no secondary objectives for this trial		
Tertiary/Exploratory		
Procedure Metrics	Number of placement attempts per patient. Tube migration.	
Safety	Adverse Events	

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a single center, non-randomized feasibility clinical evaluation that is designed to affirm the safety of the NUTRIPLACE System guidance during the placement of the Nutriseal nasoenteral feeding tubes. Data collected during this trial is designed to ensure that NUTRIPLACE System can be used to successfully place Nutriseal NETs in the desired location without guidance-related adverse events.

This study will be an in-hospital study which will follow enrolled subjects for an acute period of up to 48 hours post-placement.

4.2 END OF STUDY DEFINITION

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Candidates for this study must meet the following inclusion criteria in order to be enrolled in this trial:

- Patients must be ≥21 years of age
- Patients must require placement of a nasoenteral feeding tube
- Patients have an endotracheal tube, OR
    - Do not have an endotracheal tube but are sedated (RASS score of -2 or less) and/or obtunded (Glasgow Coma scale of9-12)
- Patients or legal authorized representative must be able to understand and adhere to all protocol procedures and be willing and able to provide written informed consent

5.2 EXCLUSION CRITERIA

Candidates for this study must not meet any of the following exclusionary criteria in order to be enrolled in this trial.

- Patients must not have a history of:
    - Esophageal varices or ulcers
    - Upper airway obstruction
    - Upper GI stenosis or obstruction
    - Trauma involving sinuses, nares face or neck that would prevent NG tube insertion
    - Deformities of the sinus cavities and/or skull base
    - Esophageal cancer or neoplasm
- Patients must not have a significant concomitant illness that would adversely affect their participation in the study
- Female patients who are pregnant or lactating

5.3 FEMALE PATIENTS WHO ARE PREGNANT OR LACTATING

A urine pregnancy test will be required to rule out pregnancy in females of child-bearing potential. For female patients with a Foley catheter, urine samples for the pregnancy test are to be taken from the sample port on the catheter.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study and do not complete the Procedure Visit. 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 demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Subjects for this trial will be recruited from the currently hospitalized and require placement of an NET tube. It is anticipated that two months will be required to treat the run-in patients and enroll the full trial cohort. Given the acute, in-hospital nature of this trial, no special measures will be needed to retain enrolled patients.

6 STUDY INTERVENTION

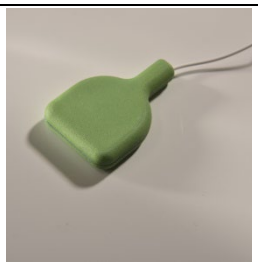
6.1 STUDY INTERVENTION(S)

The NUTRIPLACE System is composed of a dedicated mobile cart and is equipped with a battery-operated All-in-One (AIO) PC installed with the Microsoft™ Windows operating system. The AIO PC runs the NUTRIPLACE software which controls the ElectroMagnetic (EM) tracking system which includes the field generator, marking stylus, and two patient (alignment) sensors. The System also includes a printer, interface cables and a power cable for recharging the System batteries.

The NUTRIPLACE System includes 9 major components:

1. Plate sensor (patient-position angle sensor)
A thin, flat sensor positioned under the patient's upper back.

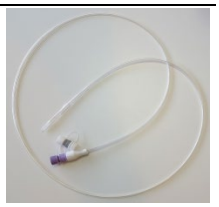
2. Reference sensor
The reference sensor is placed on the side of the chest under the patient's armpit. This sensor is used as a reference for EM tracking as well as to determine patient body width.



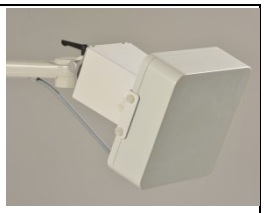
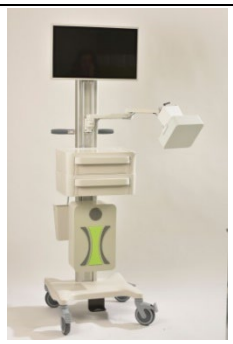
3. Reference sensor patch
A white plastic cover that is used to protect the reference sensor and to enable the attachment of the Reference sensor to the patient's armpit. The reference sensor cover is single-use only and must be replaced for each patient.

5. Marking stylus
A stylus equipped with a sensor and button, used to indicate the Suprasternal Notch and Xiphoid Process locations on the patient's chest.

6. Nasoenteral tube (NET)
A feeding tube that is passed through the nose and down through the nasopharynx and esophagus into the stomach or post-pylorus. An EM sensor is embedded within the distal tip of the NET.



7. PC and touch screen
A dedicated All-in-one computer running the Nutriplace software.

4. Field generator A rectangular electromagnetic-field generator that is attached to the Nutriplace System. The field generator is placed above the patient's chest.		**8. Nutriplace printer** Used for printing final Placement report and screenshots	
	9. Cart with handle A dedicated mobile cart housing the System components, containing drawers, wheels that can be locked and height adjustment pedal.		

A full description of the System and its use is provided in the Investigator's Brochure (Attachment 1) the NUTRIPLACE System User Manual and the NasoEnteral Tube Instructions for Use (Attachment 2). The NUTRIPLACE System will be used on enrolled subjects following the documented methods and in consideration for the investigational sites standard of care regarding the placement of nasoenteral feeding tubes.

The study of the NUTRIPLACE System is considered a non-significant risk study of an investigational medical device. The rationale supporting the non-significant risk status is included in the NSR Letter (Attachment 3).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Sufficient supplies of the NUTRIPLACE System will be provided to the investigational site directly by manufacturer, Nutriseal L.P.

6.2.2 PRODUCT STORAGE AND STABILITY

The NUTRIPLACE System does not require special storage conditions, e.g., it may be stored at room temperature. The Nutriseal NasoEnteral Tube should be stored in a clean dry location. The shelf life for the product is stable for a minimum of 6 months.

It is expected that the investigational site will store all components of the system in a secure location between uses.

6.2.3 PREPARATION AND USE

Preparation and use of the NUTRIPLACE System are discussed in detail in the NUTRIPLACE System User manual and the NasoEnteral Tube Instructions for Use (Attachment 2).

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is an open label, non-randomized feasibility trial with limited bias expected. Bias in this study will be controlled through use of an independent CEC that will review and assess relatedness of reported adverse events to the NUTRIPLACE System.

6.4 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications limited to sedatives/any medication with sedative effect, anticoagulants and prokinetic agents.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

In the event a patient is discontinued from this study for any reason, all data will be collected through the time of discontinuation as well as the reason for discontinuation.

7.2 LOST TO FOLLOW-UP

Given the acute, in hospital nature of this trial, follow-up loss of patients is not expected.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The following assessments will contribute to assessment of the NUTRIPLACE System:

- **Targeted Physical examination:** height, weight
- **Vital signs**: pulse, respiration, blood pressure, and oxygen saturation via pulse oximetry (Sp02)
- **Radiographic assessments**: Abdominal and/or thoracic X-Ray will be required following the placement of the Nutriseal NasoEnteral Tube to confirm placement location and once during the follow-up period.
- **Number of Placement Attempts per Patient:**
    - ***Replacement*** is defined as complete removal of the tube from the patient or retraction above the level of the pharynx followed by reinsertion

- ***Repositioning*** is defined as changing position of tube without complete removal of the tube

- **Tube Migration:** Retrograde migration from desired placement position
- **Assessment of adverse events**

The specific timing of data collection is defined in section 1.3, Schedule of Activities.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event is defined as any untoward medical occurrence associated with the use of the NUTRIPLACE System whether or not the event is considered intervention-related.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) will be considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Other serious Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An unanticipated adverse device effect (UADE) means 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 clinical protocol, investigator's brochure, or Instructions for Use (IFU) or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

The investigator will categorize the severity of adverse events (AEs) reported in this study using the following definitions:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.

- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

The investigator will categorize the relationship of all adverse events (AEs) reported in this study to the NUTRIPLACE System based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of device and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

In addition, AEs designated as "Definitely", "Probably" or "Potentially" related to the NUTRIPLACE System will be further categorized by the investigator to determine the relationship of the event to the NUTRIPLACE Guidance System based on the following categories:

- Events that likely resulted from insufficient information provided by the guidance system
- Events that likely resulted from inaccurate or confusing information provided by the guidance system
- Events that are not likely related to the guidance system.

8.2.3.3 EXPECTEDNESS

The investigator 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 in the IB or the instructions for use.

8.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant or upon review by a study monitor.

AEs not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to NUTRIPLACE System, and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All SAEs determined to be related to the NUTRIPLACE System will be followed to adequate resolution or stabilization.

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.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

8.2.5 ADVERSE EVENT REPORTING

Any reported AE must be reported to Nutriseal via the CRF within 48 hours of the time the Investigator becomes aware of the AE.

Any reported SAE must be reported to Nutriseal via the CRF within 24 hours of the time the Investigator becomes aware of the SAE.

If the Investigator believes that a potential UADE has occurred, Nutriseal must be contacted immediately. In addition, the investigator shall submit to the Nutriseal and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect."

Nutriseal 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.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

There is no formal statistical hypothesis for the primary endpoint of this feasibility trial. The primary endpoint is defined as procedure success, e.g., NET tube can be placed in the correct anatomical position without occurrence of guidance-related adverse events.

9.2 SAMPLE SIZE DETERMINATION

This feasibility trial will include fifty (50) patients completing the Procedure Visit (NasoEnteral Tube placement) and five operators. Each operator must complete training on one run-in subject prior to participating in this study. Patients or patients' LAR who chose not to participate after informed consent but prior to procedure, and patients who because of system malfunction or because of undiscovered or unreported physical reasons (e.g. deteriorating health, anatomical anomalies, mechanical obstruction, etc.) cannot complete the Procedure Visit (NasoEnteral Tube placement) will be considered Screen Failures, not be considered in the total patient count, but will be reported in the ITT dataset as defined below. If less than 45 patients will complete the Follow-up Visit (confirmation of tube tip anatomical location), an enrollment of another 5 patients will be considered.

9.3 POPULATIONS FOR ANALYSES

Populations that will be analyzed include the following:

- Intention-to-Treat (ITT) Analysis Dataset (i.e., all enrolled participants)
- Per-Protocol Analysis Dataset: defines enrolled patients for whom no protocol deviations were noted
- Full Cohort Dataset: includes the ITT population plus the Run-in patients

9.4 STATISTICAL ANALYSES

The procedure success will be calculated for all populations. Additional descriptive statistics will be presented as appropriate using means, standard deviations, medians and ranges for the continuous variables and as counts and percentages for categorical variables.

9.4.1 BASELINE DESCRIPTIVE STATISTICS

Baseline demographics will be tabulated and include descriptive statistics were applicable.

9.4.2 PLANNED INTERIM ANALYSES

Interim analyses will not be conducted in this trial.

9.4.3 SUB-GROUP ANALYSES

There are no planned sub-group analyses.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The consent materials contained in Attachment 4 are submitted with this protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant or his/her legal authorized representative will be asked to read and review the document. The investigator will explain the research study to the participant or legal authorized representative and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant or legal authorized representative's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants or legal authorized representatives will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participant or legal authorized representative should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant or legal authorized representative will sign the informed consent document prior to any procedures being done specifically for the study. Participants or legal authorized representatives 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 participants or legal authorized representatives 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.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

Premature stoppage of this acute feasibility study is not anticipated given the planned enrollment and non-significant risk nature of this study.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigator, their staff, and Nutriseal. 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 Nutriseal.

The study monitor, other authorized representatives of Nutriseal, representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical 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 Nutriseal requirements.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Oversight of this clinical trial will be provided by:

Principal Investigator
May Olayan, M.D.
Cleveland Clinic Foundation
2049 East 100th Street *Cleveland, OH*
Phone: 216-387-0182
olayanm@ccf.org

In addition, a Clinical Events Committee (CEC) will be convened to adjudicate adverse events reported in this trial. Activities of the CEC will be governed by a CEC charter. See description in 10.1.5 below.

10.1.5 SAFETY OVERSIGHT

A data safety monitoring board (DSMB) will not be convened for this non-significant risk study. The CEC will consist of one physician and one engineer. Due to the expected short duration of this trial, the CEC will not provide interim analysis of data, but will instead review any SAE's that occur to determine the need to halt the trial, and will adjudicate the involvement of the subject device in any AEs or SAEs. Daily monitoring of the trial is being delegated to Dr. Anat Hofshi, an employee of NutriSeal. This monitor will perform evaluation of the study conduct including informed consent, intake, execution, data recording, and reporting of AEs and SAEs. Significant deviations from protocol will be immediately reported to the Sponsor and CEC. Further, this monitor will notify the Sponsor and the CEC of any SAEs that occur and ensure all available data is provided to the CEC to evaluate whether the trial should continue.

10.1.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Nutriseal representative will conduct on-site monitoring. Given the acute nature of this clinical trial, one visit is anticipated following the capture of all trial data. During this visit, 100% source data verification will be confirmed.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

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

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 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.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the case report form (CRF) derived from source documents should be consistent with the data recorded on the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The 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.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within five (5) working days of identification of the protocol deviation. All deviations must be addressed in study source documents and recorded in the appropriate CRF. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.10 PUBLICATION AND DATA SHARING POLICY

Twelve (12) months following the completion of the study, the Investigator may publish the result of their data from the study. The Investigator shall provide the Nutriseal advanced copies of any proposed publication sixty (60) days prior to the planned publication. Nutriseal will have sixty (60) days to review the proposed publication for the purposes described below. Nutriseal may request in writing (a) the deletion of any confidential information, (b) any reasonable changes requested, or (c) a delay of the proposed publication, not to exceed ninety (90) days, in order to protect the potential patentability of any technology.

10.1.11 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. The investigator and any sub-investigators are required to disclose the following financial interests, arrangements, and payments per 21 CFR 54.4(a)(3):

- Any compensation made to the Investigator by Nutriseal of the covered clinical study in which the value of compensation could be affected by study outcome;
- A proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright, or licensing agreement;
- Any equity interest in Nutriseal, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices;
- Any equity interest in Nutriseal if Nutriseal is a publicly held company and the interest exceeds $50,000 in value; and
- Significant payments of other sorts made by Nutriseal to the Investigator of the Investigator's institution, with a monetary value of $25,000 or more, during the time the Investigator is carrying out the study and for one (1) year following the completion of the study.

10.2 ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AIO PC	NUTRIPLACE all in one computer. A substitute touch screen monitor may be used with a minimum size of 19 inch.
Anatomical landmarks	Two points on the patient's chest, one (upper) on the Suprasternal notch and the second on the Xiphoid process. These are also referred to as fiducial points.
Axial View	A view of the body, observed from legs to head of the subject.
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
EM	Electromagnetic
EN	Enteral Nutrition
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH-GCP	International Conference on Harmonization- Good Clinical Practice
IFU	Instruction For Use
IRB	Institutional Review Board
ITT	Intention-To-Treat
Marking Stylus	A Stylus equipped with a sensor, used to indicate the two anatomical landmarks (fiducial point) locations of the Suprasternal Notch and the Xiphoid Process
NET	The Nasoenteral Tube – Contains EM Sensor in the distal tip used with the NUTRIPLACE System. The NET is a feeding tube that is passed through the nose and down the nasopharynx and esophagus into the stomach or small intestine and connected to a feeding pump or bag using an ENFit Connector
NUTRIPLACE System	The NUTRIPLACE System including all sensors and software.
RASS	Richmond Agitation-Sedation Scale
SAE	Serious Adverse Event
SOA	Schedule of Activities
Software	The NUTRIPLACE Software, running on the NUTRIPLACE PC
SOP	Standard Operating Procedure
Suprasternal notch	A large, visible notch in between the neck and the collarbone
System	The NUTRIPLACE System
UADE	Unanticipated Adverse Device Effects
Xiphoid Process	An extension of the lower part of the sternum. External anatomical indication for the entry to the stomach.

10.3 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

REFERENCES

1. Milsom SA, et al. Naso-enteric Tube Placement: A Review of Methods to Confirm Tip Location, Global Applicability and Requirements. *World J Surg*. 2015;39(9):2243-52.
2. Koopmann MC, Kudsk KA, et al. A team-based protocol and electromagnetic technology eliminate feeding tube Placement complications. *Ann Surg*. 2011 Feb;253(2):287-302.
3. David Smithard, Nicholas A. Barrett , et al. Electromagnetic Sensor-Guided Enteral Access Systems: A Literature Review. *Dysphagia*. 2015; 30(3): 275–285.
4. Metheny NA. Preventing respiratory complications of tube feedings: evidence-based practice. *Am J Crit Care*. 2006 Jul;15(4):360-9.
5. Powers J, et al. Bedside Placement of small-bowel feeding tubes in the intensive care unit. *Crit Care Nurse*. 2003 Feb;23(1):16-24.
6. Taylor SJ, et al. Treating delayed gastric emptying in critical illness: metoclopramide, erythromycin, and bedside (cortrak) nasointestinal tube Placement. *JPEN J Parenter Enteral Nutr.* 2010 May-Jun;34(3):289-94.
7. Gunnar Elke, et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. *Crit Care*. 2016; 20: 117.
8. Metheny NA, Meert KL. Effectiveness of an electromagnetic feeding tube Placement device in detecting inadvertent respiratory Placement. *Am J Crit Care*. 2014 May;23(3):240-7.
9. Krenitsky J. Nutrition issues in gastroenterology, series no. 93: blind bedside Placement of feeding tubes: treatment or threat? *Pract Gastroenterol*. 2011;35(3):32–42.
10. Initial and Ongoing Verification of Feeding Tube Placement in Adults (applies to blind insertions and Placements with an electromagnetic device). *Crit Care Nurse*. 2016 Apr;36(2):e8-e13.
11. Bryant V, Phang J, et al. Verifying Placement of small-bore feeding tubes: electromagnetic device images versus abdominal radiographs. *Am J Crit Care*. 2015 Nov;24(6):525-30.
12. Arja Gerritsen, Marcel J. van der Poel, et al. Systematic review on bedside electromagnetic-guided, endoscopic, and fluoroscopic Placement of nasoenteral feeding tubes. *Gastrointestinal Endoscopy*. 2015; 8(4): 836-847.
13. Gray R, Tynan C, et al. Bedside electromagnetic-guided feeding tube Placement: an improvement over traditional Placement technique? *Nutr Clin Pract*. 2007 Aug;22(4):436-44.
14. Powers J, Luebbehusen M, et al. Verification of an electromagnetic Placement device compared with abdominal radiograph to predict accuracy of feeding tube Placement. *J Parenter Enteral Nutr*. 2011 Jul;35(4):535-9.
15. Powers J, Fischer MH, et al. Elimination of radiographic confirmation for small-bowel feeding tubes in critical care. *Am J Crit Care*. 2013 Nov;22(6):521-7.
16. Metheny NA, Meert KL, et al. Update on Effectiveness of an Electromagnetic Feeding Tube-Placement Device in Detecting Respiratory Placements. *Am J Crit Care*. 2017 Mar;26(2):157-161.
17. P.J. Kearns, C. Donna. A controlled comparison of traditional feeding tube verification methods to a bedside electromagnetic technique. *JPEN J Parenter Enteral Nutr.* 25 (2001), p. 210

Attachment 1
Investigator's Brochure

Attachment 2
NUTRIPLACE System
Instructions for Use

Attachment 3
Nonsignficant Risk Justification

Attachment 4
Informed Consent