CLINICAL INVESTIGATION TO EVALUATE REMOVAL OF THE EVOLUTION® ESOPHAGEAL STENT – FULLY COVERED (CLARITY)

Global Clinical Number 11-012

Sponsor:

MED Institute, Inc.
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USA

Summary of Revisions

Version #	Description	Date
11-012-01	Original version	11 Sept 2012
11-012-02	Modifications including inclusion of benign performance goal and revision of sample size	29 Nov 2012
11-012-03	Modifications including revision of follow-up windows	05 Mar 2013
11-012-04	Modifications including minor clarifications to inclusion/exclusion criteria and migration endpoint	11 Nov 2013

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

This clinical investigation will be conducted in accordance with the clinical investigation plan (CIP), GCP, 21CFR812, and other applicable requirements as appropriate. The CIP will be revised, as appropriate, based on new information.

Signatures:

Global Sponsor Contact:

X _____ _____
Signature DD MONTH YYYY

[redacted] _____ [redacted]
Printed Name Title

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE, CON'T

Coordinating Clinical Investigator:

I hereby confirm that I approve of this Clinical Investigation Plan (CIP) and agree to comply with its terms as laid out in this document.

X _____ _____
Signature DD MONTH YYYY

[redacted] _____ _____
Printed Name Title

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE, CON'T

Principal Clinical Investigator
I hereby confirm that I approve of this Clinical Investigation Plan and agree to comply with its terms as laid out in this document.

X _____	_____
Signature	DD MONTH YYYY
_____	_____
Printed Name	Title

CONFIDENTIALITY STATEMENT

This document shall be treated as a confidential document for the sole information and use of the clinical investigation team and the IRB.

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Appendices

1 Clinical Investigation Plan Overview

This prospective, multicenter, single-arm clinical investigation will evaluate the endoscopic removability of the Evolution® Esophageal fully covered stent. Patients may be enrolled in the study when a patient requires stenting for an obstruction caused by an intrinsic or extrinsic malignancy; refractory benign esophageal stricture; or to seal an esophageal fistula, perforation, or leak. Patients will be enrolled at up to 15 investigative sites until a maximum of 130 patients have been enrolled to ensure that 58 patients have had endoscopic stent removal attempted after an indwell time of at least 7 days, but no more than 6 months. [redacted] **Figure 1** presents a flow diagram of the study design.

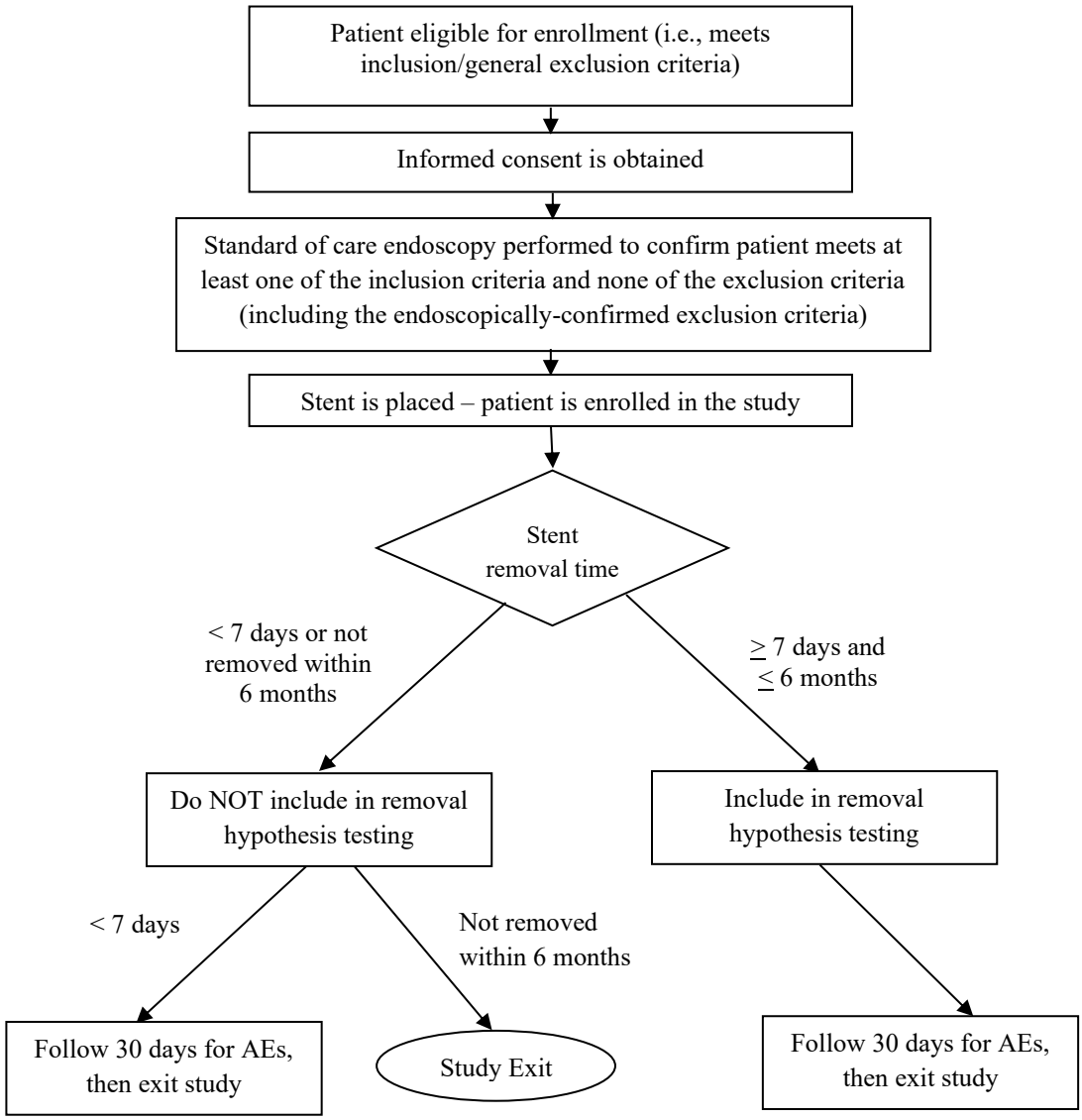

Figure 1. Study flow diagram.

2 Objectives of the Clinical Investigation

2.1 Primary Objective

The primary objective of this study is to evaluate the endoscopic removability of the stent component of the Evolution® Esophageal Stent System – Fully Covered (known as the Evolution® Esophageal fully covered stent) when used to treat patients with an obstruction caused by an intrinsic or extrinsic malignancy; refractory benign esophageal strictures; or esophageal fistulas, perforations, or leaks.

The **primary endpoint** will be the proportion of patients, of those patients in whom endoscopic retrieval is attempted after an indwell time of between 7 days and 6 months, who have successful stent removal (see Appendix C) of the Evolution® Esophageal fully covered stent. [redacted]

2.2 Additional Objectives

Other objectives for the study are to collect and evaluate additional outcome measures, including effectiveness of the stent in benign conditions, as outlined in section 5.5 Endpoints.

3 Product Description and Intended Use

3.1 General Product Description

The Evolution® Esophageal fully covered stent is a flexible, self-expanding stent constructed of a single, woven, nitinol wire (**Figure 2)**. Due to its design, the stent foreshortens as it expands. It is fully covered. [redacted] To aid in visibility under fluoroscopy, there are four radiopaque marker bands at either end of the stent. The stent has lassos, which include grasping features, at the proximal and distal ends of the stent that are used in stent repositioning and stent removal. The total length of the stent is indicated by radiopaque markers on the inner catheter of the delivery system; the radiopaque markers indicate the actual stent length when expanded to nominal stent diameter.

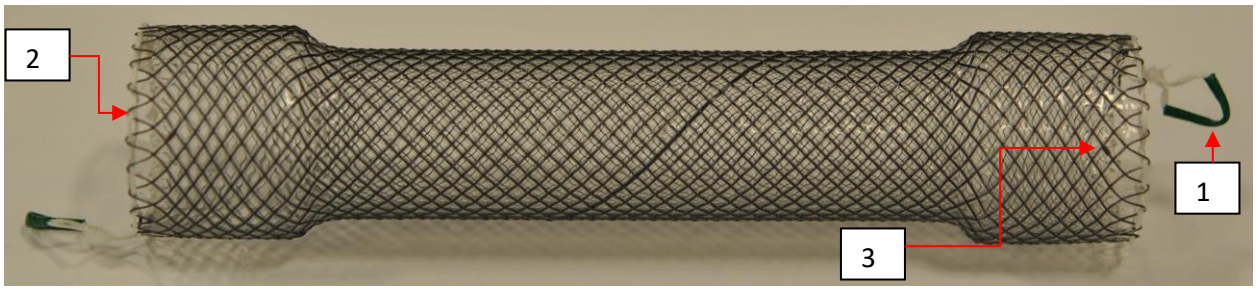

Figure 2. Photograph of the Evolution® Esophageal fully covered stent. 1= Lasso loop grasping feature, 2 = Crown, and 3 = Radiopaque marker band

The stent is mounted on an inner catheter, which accepts a 0.035 inch wire guide, and is constrained by an outer catheter. A pistol-grip delivery handle allows stent deployment or recapture (**Figure 3**).

Figure 3. Delivery system handle

3.2 Intended Use

The Cook Evolution® Esophageal Stent System – Fully Covered is indicated in this study to maintain luminal patency of the esophagus in cases of obstruction caused by intrinsic or extrinsic malignancies; refractory benign strictures; or to seal esophageal fistulas, leaks, and perforations.

3.3 Product Identification and Tracking

The Evolution® Esophageal Stent System – Fully Covered will be tracked throughout the course of the study by means of a Product Log that includes information such as serial numbers, quantity, and disposition of product. A Product Log will be maintained by each investigative site. In addition, information such as the size and lot number of products used in each patient will be recorded on individual case report forms.

The device is available in several diameters and length options as detailed in Table 1.

Table 1. Evolution® Esophageal fully covered stent dimensions

RPN	Body (mm)	Flange (mm)	Length (cm)
EVO-FC-R-18-23-8-E-CI	18	23	8
EVO-FC-R-18-23-10-E-CI	18	23	10
EVO-FC-R-18-23-12-E-CI	18	23	12
EVO-FC-R-20-25-8-E-CI	20	25	8
EVO-FC-R-20-25-10-E-CI	20	25	10
EVO-FC-R-20-25-12-E-CI	20	25	12

3.4 Instructions for Use

Refer to the manufacturer's Instructions for Use (IFU) for the following:

- Complete instructions including storage and handling requirements, preparation for use, pre-use checks, and precautions to be taken during use, after use and disposal
- Complete summary of the necessary training and experience required for use of these devices
- Complete description of the procedures involved in the use of these devices
- Contraindications, relative contraindications, and warnings for the devices

[redacted]

4 Risk Analysis and Risk Assessment

4.1 Risks and Foreseeable Adverse Events

As part of the stent implantation and removal, endoscopic procedures may also need to be performed. These procedures are generally recognized as safe, although risks have been noted with these procedures. Potential risks associated with endoscopic procedures and/or esophageal stenting and removal include, but are not limited to:

- Perforation
- Hemorrhage
- Aspiration, reflux, vomiting
- Fever, infection
- Allergic reaction (e.g., to medication)
- Hypotension
- Respiratory compromise, depression, or arrest
- Cardiac arrhythmia or arrest
- Stent misplacement and/or migration
- Tumor and tissue ingrowth and overgrowth, [redacted]
- Dysphagia [redacted]
- Esophageal ulceration and erosion
- Tear/tissue damage [redacted]
- Wire entrapment
- Nausea
- Pain
- Foreign body sensation or reaction
- Esophagitis

- Edema
- Food bolus impaction
- Gas bloat syndrome
- Sensitivity to device components
- Fistula (e.g., involving trachea, bronchi, or pleural space)
- Intestinal obstruction secondary to migration
- Mediastinitis or peritonitis
- Airway compression
- Tracheal obstruction
- Compression of adjacent structures
- Death (other than due to normal disease progression)

It is also important to note that the decision to remove or reposition the stent is based on the physician's clinical judgment. Pre-existing conditions (e.g., stricture, fistula, perforation, leak) may not be healed at the time of stent removal and may require additional intervention.

4.2 Methods to Minimize Risks

This device will be used only by trained gastroenterologists who are experienced in endoscopic procedures. Physicians who may remove the stent endoscopically will be trained on the removal procedure. Patients will be selected according to this study's labeled indication and in accordance with the inclusion/exclusion criteria outlined in this document. There are no

restrictions on the use of medications or other standard of care procedures used to maintain patient comfort and speed recovery peri-procedurally.

[redacted]

5 Design of the Clinical Investigation

5.1 Type of Investigation

This prospective, multicenter, single-arm clinical investigation will evaluate the endoscopic removability of the Evolution® Esophageal fully covered stent in patients with esophageal obstruction caused by intrinsic or extrinsic malignancies; refractory benign esophageal strictures; or esophageal fistulas, perforations, or leaks. [redacted]

Patients will be enrolled at up to 15 investigative sites until a maximum of 130 patients have been enrolled to ensure that 58 patients have had endoscopic stent removal attempted after an indwell time of at least 7 days, but no more than 6 months. A patient can be enrolled in the study when the patient requires stenting for an obstruction caused by an intrinsic or extrinsic malignancy; refractory benign esophageal stricture; or to seal an esophageal fistula, perforation, or leak. [redacted] Enrollment is expected to be completed within 24 months of initiating the study.

Figure 1 (page 8) presents a flow diagram of the study design.

5.2 Inclusion Criteria

Patient enrollment shall be based on known information at the time of procedure. It will not be considered a violation of the clinical investigation plan (CIP) if information obtained at a later date contradicts information collected at the time of procedure.

Patient may be included if *one* of the following is met:

- Diagnosed with a benign esophageal stricture [redacted]
- Diagnosed with a malignant intrinsic or extrinsic esophageal obstruction (e.g., stricture) [redacted]
- Diagnosed with a benign esophageal fistula, perforation, or leak [redacted]
- Diagnosed with a malignant esophageal fistula, perforation, or leak [redacted]

Note: Physicians will use their best estimate regarding expected time frames for endoscopic stent removal or stent replacement when considering a patient for inclusion in the study. [redacted]

5.3 General Exclusion Criteria

Patient will be excluded if any of the following are met:

- Patient is < 18 years of age
- Patient is unable or unwilling to provide written informed consent
- Patient is unable or unwilling to comply with the follow-up schedule
- Patient is pregnant, lactating, or planning on being pregnant within the next 6 months
- Patient is simultaneously participating in another investigational drug or device study [redacted]

[redacted]

- Patient that is contraindicated to upper GI endoscopy and/or any procedure to be performed in conjunction with esophageal stent placement (e.g., patients in whom endoscopy procedures cannot safely be performed)
- Patient has a medical condition or disorder that would limit life expectancy to less than the primary study endpoint or that may cause noncompliance with the protocol or confound the data analysis
- Patient has a known hypersensitivity or contraindication to study products that, in the opinion of the investigator, cannot be adequately pre-medicated [redacted]
- Patient is not a candidate for tumor reduction therapy or surgical resection

  Note: This criterion applies only to patients diagnosed with a malignant intrinsic or extrinsic esophageal obstruction, or with a malignant esophageal fistula, perforation, or leak.

5.4 Endoscopically-confirmed Exclusion Criteria

[redacted]

5.5 Endpoints

5.5.1 Primary Endpoint

Since the objective of the study is to evaluate endoscopic removability of the stent when used as intended, the **primary endpoint** will be the proportion of patients, in whom retrieval is attempted endoscopically after an indwell time between 7 days and 6 months, who have successful removal (see Appendix C) of the Evolution® Esophageal fully covered stent.

[redacted]

[redacted]

5.5.2 Secondary Endpoints

Secondary endpoints will include:

[redacted]

- **Clinical success**
  - In patients with strictures: improvement or relief of dysphagia symptoms (Appendix C) at the 7-day post-stent follow-up
  - In patients with fistulas, perforations, or leaks: seal sufficient to enable oral intake at the 7-day post-stent follow-up

[redacted]

These endpoints were chosen to supplement the primary endpoint. [redacted]

5.6 Variables to be Measured to Demonstrate Achievement of Endpoints

The primary endpoint will evaluate endoscopic removability of the Evolution® Esophageal fully covered stent. Specifically, the ability to completely remove the stent, incidence of tissue damage requiring immediate intervention, and hemorrhage requiring immediate intervention will be collected. Information regarding adverse events will be collected throughout this study during clinical assessments or telephone contact with the patients.

[redacted]

The clinical data will be collected on standardized case report forms. The schedule for assessments is summarized in Table 2 (section 7.6).

5.7 Measures to be Taken to Avoid or Minimize Bias

This study is not randomized or blinded. It is intended to prospectively collect information regarding the endoscopic removability of the Evolution® Esophageal fully covered stent.
[redacted]

6 Statistical Considerations

6.1 Hypotheses to be Tested

6.1.1 Hypothesis to be Tested in Patients with Attempted Endoscopic Stent Retrieval

Null Hypothesis: The percentage of patients, in whom endoscopic retrieval is attempted after an indwell time of at least 7 days, but no more than 6 months, who have successful removal of the Evolution® Esophageal fully covered stent is less than or equal to the performance goal of 88%.

$H_0: \gamma \leq 88\%$

Alternative

Hypothesis: The percentage of patients, in whom endoscopic retrieval is attempted after an indwell time of at least 7 days, but no more than 6 months, who have successful removal of the Evolution® Esophageal fully covered stent is greater than the performance goal of 88%.

$H_a: \gamma > 88\%$

6.1.2 Hypothesis to be Tested in Patients with Benign Indications

Null

Hypothesis: The rate of clinical success in patients with benign indications is less than or equal to the performance goal of 80%.

$H_{2_0}: \pi \leq 80\%$

Alternative

Hypothesis: The rate of clinical success in patients with benign indications is greater than the performance goal of 80%.

$H_{2_a}: \pi > 80\%$

6.2 Sample Size

The study is designed to enroll a maximum of 130 patients to ensure that 58 patients have had an attempted endoscopic stent removal after an indwell time of at least 7 days, but no more than 6 months, to evaluate the primary hypothesis (section 6.1). Patients may be enrolled at up to 15 investigative sites, with no requirements regarding the maximum or minimum number of patients able to be enrolled at any given site. [redacted]

[redacted] Cook intends to enroll a maximum of 130 patients to ensure that 58 patients have

had an attempted endoscopic stent removal after an indwell time of at least 7 days, but no more than 6 months.

[redacted]

6.3 Missing Data

[redacted] Appropriate summary statistics will be presented for the 58 patient cohort, as well as all the enrolled patients when appropriate, based on available data. Patient withdrawals and lost to follow-up will be tabulated and assessed for their potential impact on the study results. Specifically, if any patients withdraw or become lost to follow-up prior to the analysis of the 58 patients with stent removal, then the primary endpoint will be examined for the sensitivity of the results on these missing data via tipping point analysis. [redacted]

6.4 Site-level Poolability

At the final analysis, poolability of data from multiple sites will be verified by examining the primary and secondary endpoints among sites as well as important patient baseline characteristics. Site-level poolability will be considered appropriate provided that these measures are similar among sites.

It is expected that some sites may have too few patients to provide reasonable site-level estimates of primary, secondary, and baseline measures. Pooling of this information will be explored based on hospital size (large versus small), site enrollment (large versus small), type of hospital (community versus teaching), and other group-wise strategies.

It is recognized that patient baseline characteristics may differ among sites, with some sites routinely treating patients with more severe disease progression. It is anticipated that the primary and secondary endpoint measures may be related to covariates that reflect this disease

progression, which are in turn related to outcome. Thus, observed site-specific differences among the primary or secondary endpoints will be checked for confounding with other measured covariates (e.g., age, sex). This can be accomplished using regression models (linear and logistic where appropriate) that include site and other measured covariates as independent variables.

Should one or more sites be found to differ significantly from the rest, then subsequent analyses may include the discriminating covariate or a covariate to distinguish between the unusual site(s) and those sites that are considered poolable.

6.5 General Analysis

The first 58 patients with attempted endoscopic stent removal (see Appendix C for definition) after an indwell time of at least 7 days, but no more than 6 months, will be included [redacted]. It is recognized that additional patients enrolled prior to the 58th attempted endoscopic stent removal may also have stent removal attempted prior to exiting the study. Those additional patients will be followed until reaching a study endpoint; however, these patients will not be initially included [redacted]

Secondary endpoints may be analyzed separately and/or together for those patients with attempted stent removal compared to those patients without attempted stent removal. [redacted]

Descriptive summaries will be provided where appropriate for each of the primary and secondary variables. In general, summaries will be complete over the total population. Continuous variable summaries will include the number of subjects (N), mean, standard deviation, minimum, and maximum. Categorical variable summaries will include the frequency and percentage of subjects who are in the particular category. In general, the denominator for the percentage calculation will be based upon the total number of subjects with the measurement for the total population and by treatment group, unless otherwise specified.

6.6 Limitations of the Investigation

The study is limited by the small sample size, but allows for calculations of appropriate summary statistics. There is also the possibility that patients will reach study completion of data collection prior to stent removal, due to one of the events described in Section 7.10 (e.g., death, withdrawal, reached 6 months without stent removal). [redacted]

7 Methods

7.1 Subject Consent

Patients who meet one of the inclusion criteria and none of the general exclusion criteria will be invited to participate in this investigation. All patients eligible for entry into the investigation will have the clinical investigation plan explained to them, as well as potential risks and benefits of their participation in the investigation. Each patient who agrees to participate will be required to sign an informed consent document prior to the procedure. A baseline evaluation to collect data should include, but is not limited to, symptoms of the condition (e.g., pain, nausea), applicable past or current medical conditions, and patient's dysphagia score. Some inclusion/exclusion criteria [redacted] may require evaluation immediately prior to stent placement to confirm eligibility into the study.

7.2 Medications

Pre-procedural, procedural, and post-procedural/discharge medication and therapy should be based upon clinical indication and underlying disease (i.e., standard of care). Information regarding use of acid suppression therapy and tumor reduction therapy should be captured at baseline, discharge, and throughout follow-up.

7.3 Stent Placement Procedure

Please refer to the manufacturer's IFU for stent and delivery system instructions, including general use information, patient preparation, procedural needs, wire guide use and selection, stent size selection, stent expansion/stent deployment, and delivery system removal. Dilation should be completed, as necessary, to allow complete evaluation of the lesion prior to delivery of the stent. Confirmation that the patient meets one applicable inclusion criterion, and none of the exclusion criteria [redacted] must be obtained prior to introduction of the stent. The IFU recommends assessment and pre-dilation of the stricture, as necessary [redacted] Pre-dilation can occur over several sessions per the physician's discretion prior to stent placement. There is a lasso loop with a grasping feature on both ends of

the stent to allow repositioning of the stent during the procedure, if needed (e.g., in the event of incorrect placement). [redacted]

At the time of the stenting procedure, the following information should be recorded, at a minimum:

- Lesion characteristics
- Stent information
- Reason/indication for stent placement
- Ability to deliver and accurately place the stent
- Device integrity
- [redacted]Need for repositioning [redacted]
- Adverse events (including serious events) occurring during the procedure

7.4 Point of Enrollment

Point of enrollment will be based on the intent-to-treat population, and is defined to include any patient for whom the treatment procedure is initiated. More specifically, once the delivery system of the study device (Evolution® Esophageal Stent System – Fully Covered) has been inserted into the patient, this patient would be included in the intent-to-treat population. Cook intends to enroll a maximum of 130 patients to ensure that 58 patients have had endoscopic stent removal attempted after an indwell time of at least 7 days, but no more than 6 months. The first 58 patients with attempted endoscopic stent removal after an indwell time of at least 7 days, but no more than 6 months, will be included [redacted]. Additional analyses on remaining endpoints may be performed on all enrolled patients, as applicable, including an analysis on clinical success of the stent in benign conditions.

7.5 Post-stent Placement Procedure and Discharge

Patients should be observed for development of any complications of endoscopy procedures, esophageal dilation, or stent placement. [redacted]

[redacted]

Patients should be discharged according to institutional standards. At the time of discharge, information including, but not limited to clinical symptoms (e.g., pain, nausea) and adverse events (including serious events) occurring since the procedure should be recorded.

7.6 Follow-up Post-stent Placement

Patients will be followed after stent placement according to the schedule below unless the stent is removed (surgically or endoscopically), a non-study stent is placed, or other study exit (e.g., death, withdrawal, lost to follow-up) has occurred:

Clinic visit	7 days (range 5-12 days)
Telephone	1 month ± 7 days
	2 months ± 7 days
	3 months ± 7 days
	4 months ± 7 days
	5 months ± 7 days
	6 months ± 7 days

If a patient completes a required visit outside of the prescribed follow-up window, it will be recorded as a deviation from the clinical investigation plan.

Patients enrolled in the study will be followed an additional 30 days following endoscopic stent removal, unless replaced with another non-study stent. If the study stent is surgically removed (e.g., during esophagectomy), the patient will immediately exit the study. If a non-study stent is placed (either before or after stent removal), the patient will immediately exit the study (note: overlapping stents is not recommended per the IFU). If the stent removal procedure occurs at the 6- month follow-up, patients will be followed an additional 30 days following the stent removal procedure. The data collection schedule is provided in Table 2.

For all telephone contacts, a prescribed script is recommended to collect the required data. At least three attempts to contact the patient should be made and documented in the study source documents. If the patient still cannot be reached it may be considered a missed visit/telephone contact. Of note, data may be collected at a clinic visit instead of a telephone call if preferred by the patient and/or physician.

Table 2. Data collection schedule

Data collection schedule[1]	**Pre-procedure**	**Stent placement procedure/discharge**	**7-day**[2] *(5-12 days)*	**1-month**[2] *(23-37 days)*	**2-month**[2] *(53-67 days)*	**3-month**[2] *(83-97 days)*	**4-month**[2] *(113-127 days)*	**5-month**[2] *(143-157 days)*	**6-month**[2] *(173-187 days)*	**Stent removal**	**30 days post-stent removal**
Informed Consent	X										
Inclusion/ Exclusion	X	X									
Medical History	X										
Lesion Characteristics		X									
Dysphagia Score	X		X	X	X	X	X	X	X	X	X
Endoscopy[2]		X								X	
Radiographic Assessment[2]		X[3]								X[3]	
Telephone Contact[4]				X	X	X	X	X	X		X
Clinic Visit[4]	X	X	X							X	

[1] If a non-study stent is placed (e.g., inside the study stent or after study stent removal) or if the study stent is removed surgically, patient will exit the study immediately. If study stent is completely removed endoscopically and not replaced, patient will be followed for 30 days. If stent is not completely removed and non-study stent is not placed, patient will be followed until patient reaches 6-month follow-up or stent is completely removed.
[2] Additional endoscopy and/or radiographic assessment (e.g., X-ray) should be performed if clinically indicated (e.g., lack of marked improvement in dysphagia score, significant pain, suspected stent migration). Additional X-rays may be warranted in patients at higher risk for migration.
[3] If stent placed for fistula, perforation, or leak, radiographic assessment (e.g., barium swallow) should be performed to confirm successful sealing of the lesion after stent implantation and to confirm lesion closure following stent removal.
[4] Patient will be requested to provide information regarding clinical symptoms (e.g., dysphagia) and adverse event information since the last contact, if applicable, during each telephone contact and clinical visit during the patient's study participation. Adverse events should also be reported upon awareness of the event if between telephone contacts and clinical visits.

For patients with a fistula, perforation, or leak, documentation of the original lesion closure should be obtained following stent removal (e.g., barium swallow), even if the original lesion is not identified using endoscopy at stent removal.

Additional endoscopy and/or X-rays should be performed according to standard of care if clinical symptoms persist/recur (e.g., lack of marked improvement in dysphagia score, significant pain, suspected migration). Additional X-rays may be warranted in patients at higher risk for migration (e.g., patients undergoing radiation/chemotherapy, patients with gastric surgery resulting in altered anatomy). Symptoms resulting in additional endoscopies should be recorded as adverse events.

At follow-up, the following information should be recorded, at a minimum:

- Dysphagia score
- Patient's resumption of oral intake
- Current clinical symptoms (e.g., pain, nausea)
- Adverse events (including serious events) since last contact

7.7 Stent Repositioning

A patient may have the stent repositioned, when it is clinically indicated (e.g. sub-optimal placement after initial placement procedure, resulting in patient pain or discomfort). Please refer to the manufacturer's IFU for information regarding stent repositioning. There is a lasso loop with a grasping feature on both ends of the stent to allow stent repositioning. [redacted] If the stent is repositioned, the patient will continue to be followed according to the study schedule.

If the stent is repositioned after discharge, the following information should be recorded, at a minimum:

- Reason for repositioning
- Dysphagia score (prior to stent repositioning)
- Ability to reposition stent in desired position
- Device integrity
- Adverse events (including serious events) since last contact and during procedure to reposition stent

7.8 Stent Removal

Patients will have the stent removed when it is clinically indicated based on the physician's clinical judgment. Please refer to the manufacturer's IFU for information regarding stent removal. The indwell time may be different depending on the indication for stent implantation.

[redacted]

[redacted] There is a lasso loop with a grasping feature on both ends of the stent to allow stent removal. If the stent is endoscopically removed, the patient will be followed for 30 days post-stent removal unless a new, non-study stent is placed. If the stent is removed surgically (e.g., during esophagectomy), the patient will exit the study immediately.

If the stent is unable to be completely removed during the initial removal procedure, the patient will continue to be followed until the stent (or remainder of the stent) is removed, until an additional stent is implanted, or for 6 months after the initial stenting procedure, whichever comes first.

If the stent is endoscopically removed, the following information should be recorded, at a minimum:

- Reason for removal
- Dysphagia score (prior to stent removal)
- Ability to completely remove stent
- Device integrity
- Adverse events since last contact and during removal procedure (including serious events and visible tissue damage or hemorrhaging requiring immediate intervention)

7.9 Duration of Study and Subject Participation

Patient recruitment should be completed within 24 months of initiating the study. Follow-up data will continue to be collected for six months after stent deployment for each patient in the study, unless a patient exits the study as discussed below (reminder: the patient will be followed for an additional 30 days if the stent is removed at the 6-month follow-up).

7.10 Study Exit

A patient will be considered to have exited the study when one of the following has occurred:

- Voluntary withdrawal
- Lost to follow-up
- Death
- 30 days post endoscopic stent removal
- Stent is surgically removed (e.g., during esophagectomy)
- Non-study stent is implanted (e.g., inside study stent or after study stent is removed)
- 6 months if the stent has not been removed or replaced

After a patient exits the study, the physician may continue to follow the patient per the institution's standard of care. No additional data will be submitted to the data coordinating center once a patient has exited the study.

7.11 Criteria and Procedures for Withdrawal

A patient may decide to withdraw from the investigation at any time either before or after undergoing the procedure without prejudice or loss of care. The patient should notify the investigator of his/her desire to withdraw. The investigator will notify the sponsor. The investigator may also decide to withdraw the patient from the investigation at any time based on medical judgment. In these instances, the appropriate study visit and study termination data should be submitted to the data coordinating center, and will include the reason why the patient has been withdrawn from the study.

Patients who withdraw consent after treatment will be followed until the time of their withdrawal. No patient will be removed from the study unless the patient has withdrawn his/her consent before treatment or no treatment was ever attempted.

In the event a patient is lost to follow-up or cannot be contacted for post-treatment assessments, every effort will be made to locate the patient, and these efforts will be documented. If the patient cannot be located, a lost to follow-up entry will be submitted.

8 Deviations from Clinical Investigation Plan

Investigators are not allowed to deviate from this CIP without prior authorization by the sponsor except under emergency situations when necessary to preserve the rights, safety, and well-being of human subjects.

Deviations (failures to follow requirements of the CIP) and non-compliances (failures to follow applicable regulations) will be recorded together with an explanation. Deviations or non-compliances that impact the rights, welfare, or safety of patients shall be reported to the sponsor and IRB as required and as soon as possible.

If appropriate, corrective and preventive actions will be discussed by the sponsor, investigator, and/or the IRB to determine a suitable course of action.

9 Data Collection and Reporting

9.1 Electronic Case Report Forms (eCRF system)

Patient data will be collected and entered by the investigative site onto an electronic case report form (eCRF) through an electronic data capture (EDC) system. This is a secure, web-based system, allowing those with permission to access data from any location at any time. Source data are to be retained for data entered into the eCRF system. Site personnel are required to have

unique login names and passwords in order to enter patient data. In accordance with 21 CFR Part 11, the eCRF system creates a secure, computer-generated, time stamped audit trail to record the date and time of operator entries and actions that create, modify, or delete electronic records.

9.2 Data Reporting

Progress reports and a final report at the conclusion of the clinical investigation will be submitted by the investigators and sponsor to the IRBs as required by local regulations.

10 Data Management and Quality Assurance

10.1 Data Entry and Quality Assurance

Each principal investigator or appropriately trained designee shall enter the clinical data into the electronic data capture system. Investigators will provide all applicable clinical data and documentation to the sponsor. Patient data and documents pertaining to the investigation will be kept and archived by the sponsor. Data will be reviewed for missing data, data consistency, and reasonableness of responses. Discrepancies will be resolved through a formal query process involving direct contact with investigators or research coordinators. The data coordinating center is responsible for database management, data verification, and data archiving and retention.

As needed to assist the sponsor in its research (e.g., during evaluation of an adverse event), data will be accessible to the sponsor, the participating investigators, the manufacturer, and companies or individuals the sponsor authorizes.

10.2 Data Monitoring Arrangements

Written procedures for monitoring the investigation are maintained by the data coordinating center and can be found in Appendix B.

11 Safety Monitoring and Procedures for Reporting Adverse Events

11.1 Safety Monitoring

A Data Safety Monitoring Board (DSMB) consisting of independent physicians and at least one independent statistician, who are not investigators in the investigation, and who do not have a perceived conflict of interest with the conduct and administration of the investigation, will be convened on a regular basis to evaluate investigation progress and review adverse events.

Regularly scheduled review/monitoring of patient data will be conducted at the data coordinating center, in part, for identification of adverse events and assurance that they are correctly reported to the DSMB.

11.2 Adverse Event Reporting

Adverse events are to be reported to the data coordinating center using the appropriate case report form. In cases of adverse device effects or serious adverse events, completed forms should be submitted to the data coordinating center as soon as possible upon knowledge of the event.

The data coordinating center will review the information submitted for possible reporting to the sponsor. The sponsor shall, if required according to applicable regulations, report the event to the appropriate regulatory authority. If indicated, all investigators and sites will be notified by the sponsor. The investigator or designee will notify his/her IRB of applicable events according to institutional guidelines.

12 Early Termination or Suspension of the Investigation

Any decision to suspend enrollment or terminate the investigation will be made in conjunction with the sponsor, and the local IRB, if applicable. If a decision to terminate the study is made, all patients already treated will be followed for the duration of their participation in the study.

13 Ethical Considerations

The investigator is responsible for obtaining approval of this clinical investigation by the relevant IRB at his/her associated institution; the investigation will not begin until approval of the IRB has been obtained. The investigator is responsible for complying with requirements imposed by the IRB and/or regulatory authority. Furthermore, the investigator will ensure that regulations concerning the conduct of clinical data collection and data protection are followed.

14 Publication Policy

Publication policy, rights, and obligations for this investigation have been negotiated, detailed, and defined in the Investigation Contractual Documents and Agreements with the investigation site and investigators.

15 Trial Administration and Investigators

Contact information for the sponsor, data coordinating center, and monitor are provided in Appendix A.

15.1 Approvals and Agreements

The sponsor, coordinating investigator, and principal clinical investigators for each site shall agree to this document and any modifications. A justification for any modifications will be documented. Approval and agreement will be indicated by signing and dating the CIP signature page.

15.2 Investigators

A list including the coordinating investigator and principal clinical investigators along with their contact information and respective site information will be maintained at the data coordinating center and will be available upon request. All contact information will be updated periodically and maintained by the data coordinating center.

15.3 Insurance

Insurance for the study will be obtained by the sponsor prior to enrollment of the first patient.

[redacted]

[redacted]

[redacted]

APPENDIX A

Contact Information

Sponsor
MED Institute, Inc.
1 Geddes Way
West Lafayette, IN 47906

[redacted] jkerr@medinst.com

Manufacturer
Cook Ireland LTD.
O'Halloran Road
National Technology Park
Limerick, Ireland

[redacted] Jacinta.Kilmartin@CookMedical.com

Data Coordinating Center
MED Institute, Inc.
1 Geddes Way
West Lafayette, IN 47906

[redacted] mcutler@medinst.com
ssnyder@medinst.com

Monitor
MED Institute, Inc.
1 Geddes Way
West Lafayette, IN 47906

[redacted] jkerr@medinst.com

APPENDIX B

Written Procedures for Monitoring Clinical Investigations

A. Selection of the monitor.

Designated by the sponsor to oversee the investigation, the monitor may be an employee of Cook, an employee of a monitoring organization (CRO), or an independent contractor or consultant. The monitor shall be qualified by training and experience to monitor the investigation in accordance with all applicable regulations and standards for conducting clinical investigations.

B. General duties of the monitor.

The monitor must ensure that the investigation is conducted in accordance with:

1. The signed investigator agreement.
2. The clinical investigation plan (CIP).
3. Any conditions imposed by the IRB or regulatory authority.
4. The requirements of the applicable regulations and standards.

C. Reports by the monitor to the sponsor.

1. Any non-compliance with the items listed above. In the event that the investigator is not complying with the requirements outlined above, it is the sponsor's responsibility to secure compliance.
2. Any adverse events or effects that are potentially reportable to a regulatory authority.

D. Initiating the investigation.

Prior to initiating any clinical use of the device, the monitor or sponsor representative will participate in a pre-investigation or initiation visit with each investigative site. At a minimum, the following items shall be addressed during the site initiation visit:

- Provide training to investigator on his/her responsibilities per the investigator agreement, applicable laws, regulations, and standards; and
- Provide training to investigator that the IRB approval letter and informed consent/patient information is on file before initiation of the clinical investigation.

Additionally, training may be provided to the investigator on:

- The regulatory status of the device/product(s) and the requirements for the accountability of same;
- The nature of the CIP;
- The requirements for an adequate and well-controlled clinical investigation;

- His or her obligation to obtain informed consent in accordance with applicable regulations;
- His or her obligation to ensure continuing review of the clinical investigation by the IRB in accordance with conditions of approval and applicable regulations and to keep the sponsor informed of such IRB approval and subsequent IRB actions concerning the investigation;
- The importance of access to an adequate number of suitable subjects to conduct the investigation;
- The importance of adequate facilities for conducting the clinical investigation; and
- The importance of sufficient time from other obligations to carry out the responsibilities to which the investigator is committed by applicable regulations.

E. During the course of the investigation, at the direction of the Project Manager, the monitor should visit the site frequently enough to ensure that:

- The facilities and research staff used by the investigator continue to be acceptable for purposes of the clinical investigation;
- The applicable version of the CIP and agreements are being followed;
- Changes to the CIP, informed consent/patient information have been approved by the IRB and/or reported to the sponsor and the IRB;
- Accurate, complete, and current records are being maintained;
- Accurate, complete, and timely reports are being made to the sponsor and IRB; and
- The investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.

As appropriate, the following tasks could be performed during periodic visits:

- Device/product accountability review;
- Adverse event review to ensure that events are appropriately reported within the time periods required by the sponsor, CIP, IRB, and applicable regulatory requirements; and
- Source data verification per the monitoring plan to determine that:
    - Informed consent/patient information has been documented in accordance with applicable regulations and expectations of the local IRB;
    - The information recorded in the case report forms (paper or electronic) is complete, accurate, and legible;
    - There are no omissions in the CRFs of specific data elements, such as the administration to any patient of concomitant test articles or the development of an intercurrent illness;

- Missing visits or examinations are noted; and
- Subjects failing to complete the clinical investigation and the reason for each failure are noted.

F. Records of the monitor.

The monitor shall prepare and maintain records of each initiation visit and each periodic visit, general site contact, or discussion. These will include:

1. Date, name, and address of the investigator, and names of other staff members present at each meeting.
2. A summary of the findings of the visit.
3. A statement of any action taken by the monitor or investigator to correct any deficiencies noted.
4. The monitor shall immediately notify the sponsor of any conditions of non-compliance with the CIP, conditions of IRB or regulatory authority approval, or the applicable regulations.

APPENDIX C

Definitions

Attempted stent removal/retrieval: an endoscopic procedure in which one of the following occurs:

1) Removal is attempted by grasping the green lasso or other portion of the stent with the intention to remove the stent, or
2) Removal is intended, but the subject is not considered to be a candidate for safe endoscopic stent removal (i.e. endoscopic removal is felt to be not possible or not safe)

Clinical success, for patients with obstruction caused by an intrinsic or extrinsic malignancy or patients with a refractory benign esophageal stricture: improvement or relief of dysphagia symptoms at the 7-day post-stent follow-up

Clinical success, for patients with a fistula, perforation, or leak: seal sufficient to enable oral intake at the 7-day post-stent follow-up

Dysphagia score:

0 = able to eat a normal diet
1 = able to eat some solid food
2 = able to eat some semi-solid food only
3 = able to swallow liquids only
4 = inability to tolerate any oral intake

Significant dysphagia ≥ 2

Dysphagia, improvement: a decrease in the dysphagia score by at least 2

Dysphagia, relief: complete relief of dysphagia (i.e., dysphagia score of 0)

Stent migration: migration of the stent such that it is no longer covering treated lesion

Stent removal-related adverse events: an adverse event directly related to the endoscopic removal of the stent. These events include esophageal perforation, esophageal tears, and esophageal bleeding requiring immediate intervention. If these conditions were present prior to stent placement, any worsening due to stent removal would be considered related to the removal procedure. However, an adverse event identified during the removal procedure that was not caused specifically by removing the stent will be reported separately. For example, an ulceration or perforation that arose during implantation would not be considered as associated with

removal. Also, events caused by either applying or removing a method of supplemental fixation will not be considered related to stent removal.

Successful stent removal: one in which the Evolution® Esophageal fully covered stent

1) Is completely removed from the patient during a single endoscopic procedure with the wire mesh integrity maintained such that the stent can be removed in one contiguous piece, and
2) Has no tissue damage or hemorrhage visible during the retrieval procedure that is both:
    a. Related to endoscopic stent removal and
    b. Requires immediate treatment

[redacted]

Technical success: a stent successfully delivered and placed at its intended location at the end of the procedure (note: adjustments made during the procedure are not considered a technical failure)

Definitions for the following terms are not provided in this CIP, but can be found in the applicable regulations:

Adverse event
Adverse device effect
Device deficiency
Serious adverse event
Serious adverse device effect
Unanticipated adverse device effect
Unanticipated serious adverse device effect