MSK PROTOCOL COVER SHEET

A Prospective Phase II Trial to Evaluate Esophageal Reinforcement with ACell Gentrix Surgical Matrix: a degradable biologic scaffold material

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Clinical Problem:

Esophageal anastomoses after esophagectomy or gastrectomy for cancer are complicated by anastomotic leak in 8-15% of cases at this institution (per verbal communication with Dr. N. Rizk and Dr. D. Coit based on our institutional esophageal and gastric databases)(LaFemina et al., 2013; Rizk et al.). Leaks have potentially devastating effects and can lead to prolonged hospital stay, the need for additional procedures such as interventional radiology-placed drains, additional operative procedures such as exploratory laparotomy to irrigate and place drains, intensive care unit monitoring for those who develop sepsis, and for some, death as a result of sepsis and multi-organ failure. For those who are eventually discharged home, the development of other long-term effects such as anastomotic stricture require additional and sometimes multiple procedures such as stenting or anastomotic dilation by our gastroenterologists. This is not to mention the high associated costs associated with the additional hospital time and procedures needed to care for these patients. (see below)

Hospital charges on 6 random esophagectomies +/- a leak (courtesy of Dr. N. Rizk):						
Leak:	$82,815	$109,229	$550,612	$96,470	$113,112	$73,853
No Leak:	$55,863	$44, 535	$48,425	$91,715	$77,573	$59,553

Over the years, although attempts have been made to decrease the leak rate for esophagectomy and gastrectomy (proximal or total) by altering surgical technique or by buttressing the anastomosis with stents or other covering materials/devices, the results have been unfruitful in improving leak rate.

Proposed Intervention and Objective:

Preliminary studies have evaluated the use of a novel new biologic scaffold material that functions as a degradable extracellular matrix (ECM) that supports the regeneration of injured or missing tissue called Gentrix. This biologic scaffold material is composed of an extracellular matrix derived from porcine small intestine and urinary bladder and has been shown to promote site-specific, constructive tissue remodeling in preclinical and clinical applications for a number of body systems including the esophagus(Nieponice et al.). This Urinary Bladder Matrix (UBM), acts by recruiting native stem cells and progenitor cells to the extracellular matrix material, thus promoting regeneration of native tissue and site-specific remodelling in a process that includes complete degradation of the scaffold in 60-90 days with resultant reconstruction of tissues devoid of inflammation or scar tissue(Nieponice et al.). ACell currently markets UBM under the brand-name of Gentrix. We propose the use of ACell Gentrix Surgical Matrix PSM (“Gentrix PSM”) for reinforcement of esophageal anastomoses in patients undergoing esophagectomy, proximal gastrectomy (PG) or total gastrectomy (TG). We hypothesize that by providing a biologic scaffold at

the site of anastomosis and healing tissue, this will enhance the integrity of native tissue and promote regeneration, reducing the incidence of anastomotic leak without causing stricture.

Patient Population:

All patients who are scheduled to undergo potentially curative esophagectomy, proximal gastrectomy or total gastrectomy for cancer at Memorial Sloan-Kettering Cancer Center and participating sites will be approached to participate in the study.

Design:

Patients undergoing esophagectomy, PG or TG, via open or minimally-invasive approach, will receive a standard anastomosis reinforced with Gentrix PSM placed extraluminally. Patients would then be followed postoperatively for evidence of anastomotic leak. One routine contrast swallow study with barium, Gastrografin or Omnipaque will be performed at postoperative day 4-10. Leaks will be recorded both radiographically and clinically. Patients will continue to be followed for 90 days +/- 14 days postoperatively for evidence of stricture formation, a secondary endpoint of the study.

Time to Completion:

We plan to accrue 86 patients 76 of which will be accrued at MSK We expect that accrual will last about 20 months. With follow up of 90 days (+/- 14 days) to evaluate for stricture, we expect the total study time will be 24 months.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

1. To determine if reinforcement of esophageal anastomoses with Gentrix PSM decreases the rates of anastomotic leak. Anastomotic leak will be assessed by clinical observation and one postoperative contrast study (thin-barium, Gastrografin or Omnipaque swallow) on postoperative day # 4-10.

Secondary Objective

1. Assess stricture formation clinically and by determination of dysphagia score at 90 days postoperatively.
2. Examine cost metrics associated with all patients enrolled.

3.1 BACKGROUND AND RATIONALE

3.2 Overview

Bowel resection and anastomosis are among the most carefully taught and heavily investigated procedures performed by surgeons. The goal is to restore intestinal continuity after resection of a portion of the bowel, enabling resumption of normal bowel function. Despite multiple efforts to optimize surgical technique over decades, including careful tissue handling, adequate mobilization to minimize tension, efforts to maximize blood supply, postoperative nasojejunal decompression, and development of improved stapling devices, devastating complications of anastomotic leak and stricture formation still occur and incidence rates have not been significantly reduced(Doglietto et al.). The esophagus differs from other segments of the GI tract in that it lacks an outer serosal layer, which is the true strength layer in other segments. Additionally, the blood supply of the esophagus is segmental in nature without the high degree of anastomotic flow as is present in the stomach and small and large intestine. Esophagogastric anastomoses are therefore particularly high-risk, with leak rates varying widely in the literature and ranging up to 26% reported in the literature(Kim and Takabe; Neutzling et al.; Pacelli et al.). At our institution, leak rate is currently between 8-15% (per verbal communication with Dr. N. Rizk and Dr. D. Coit based on our institutional esophageal and gastric databases).

Anastomotic leaks are defined both clinically and radiographically. A clinical leak is defined by the appearance of enteric contents in an operatively-placed drain near the anastomosis or in a percutaneous drain placed post-operatively to evacuate a peri-anastomotic collection. A radiographic leak is one detected on cross-sectional imaging or by a contrast swallow study showing extravasation of oral contrast at the anastomosis. While patients undergoing bowel resection for benign disease are at risk of anastomotic leak, those undergoing surgery for cancer are at even greater risk as they often have poor nutrition and are subject to perioperative chemotherapy and radiation therapy. Anastomotic leaks result in prolonged hospitalization, immense health care costs, repeat procedures, and decreased quality of life, and in cancer patients, decreased survival(Yoo et al.). Patients who experience an anastomotic leak have 3x higher perioperative mortality than those who do not. Of those who survive the perioperative period, their long-term survival is also drastically reduced compared to patients who do not experience a leak(Mitchell).

Current techniques for esophageal anastomosis include hand-sewn and stapled closures with linear or circular stapling devices. Stapled closures are generally end-to-side if circular staplers are employed or side-to-side if linear staplers are used. Use of a linear stapler results in a remaining defect that must be sutures closed. All of these techniques are acceptable and choice depends on surgical approach and surgeon preference. No single technique has been definitively shown to be superior to the others.

3.3 Preliminary Data

We have performed a pilot study of 28 patients undergoing total gastrectomy via open or minimally-invasive approach to determine the feasibility of extraluminal reinforcement of the esophagojejunal anastomosis with Gentrix. In this series of patients we determined that this technique is feasible in both open and minimally-invasive procedures and that it adds essentially no time to the procedure and introduces no toxicity or side effects. Of the 28 patients, 1 experienced a clinical anastomotic leak for a rate of 3.6%.

3.4 Study Rational / Purpose

Given the feasibility of this technique and the encouraging preliminary results, the current study is proposed to determine if reinforcement of esophageal anastomoses with ACell Gentrix PSM will the reduce rate of esophageal anastomotic leak.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

Eligible patients at MSKCC and participating sites who are candidates for curative resection of esophageal or gastric cancer (requiring total gastrectomy (TG), proximal gastrectomy (PG) or esophagectomy) will be consented pre-operatively. Patients will undergo standard resection and gastrointestinal anastomosis and will then have reinforcement of the anastomosis with Gentrix PSM. Patients undergoing esophagectomy, PG or TG will be evaluated with one routine postoperative contrast swallow study at post-operative day #4-10.

4.3 Intervention

Surgical intervention will proceed in standard fashion via open or minimally-invasive approach. If a minimally-invasive approach is utilized, the Gentrix will be inserted through the 10-12 port and prepared for laparoscopic insertion according to approved measures. Gastrointestinal anastomoses would be performed in standard fashion with stapled technique or hand-sewn, followed by reinforcement by wrapping the anastomosis circumferentially with a strip of Gentrix Surgical Matrix PSM 4x12cm (PSM0412). The material would be positioned with the lamina propria surface apposed to the anastomosis itself and the basement membrane surface facing out. The cuff of Gentrix PSM would then be tacked in place with interrupted absorbable sutures.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

5.2 Background

ACell Gentrix devices are an extracellular matrix scaffold derived from porcine urinary bladder matrix (UBM). The bladder is harvested and processed to remove the muscular and submucosal tissue layers. UBM is disinfected, packaged, and sterilized via electron beam radiation. This yields a non-crosslinked, completely resorbable, acellular extracellular matrix scaffold, containing naturally-occurring collagens and proteins and maintains an epithelial basement membrane surface.

UBM is unique in that it contains a collection of proteins arranged in a natural three-dimensional structure unlike other synthetic materials. UBM maintains an epithelial basement membrane, and contains numerous collagens, laminin, growth factors, and glycosaminoglycans.

UBM was tested against liver and small intestine ECM scaffolds, which unlike UBM do not contain a surface with composition and morphology consistent with that of an intact basement membrane complex. The UBM basement membrane complex survives processing, and the structure was shown to modulate in vitro cell growth patterns.

The UBM intact basement membrane surface is theorized to contribute to epithelial and progenitor cell attachment and proliferation. The lamina propria surface may promote integration of host connective tissues from the wound bed into the scaffold.

Previous work has shown that the UBM completely incorporates into the surrounding tissue and modulates the healing process which leaves new tissue where scar tissue formation is normally expected. The result is constructively remodeled, site-specific tissue for a variety of medical procedures. UBM is an acellular material and therefore does not lead to pronounced inflammation at the implantation site as shown in dog models and in humans. UBM was demonstrated to facilitate esophageal healing after full-thickness resection in dogs and after extensive endoscopic mucosal resection in humans (Badylak et al.; Nieponice et al.). In the work by Badylak, patients underwent intra-luminal placement of Gentrix after ECM and follow up endoscopies were done at 2 weeks, 5 weeks, 10 months and 13 months post surgery. The entire resected area was covered by normal esophageal epithelium without stricture formation. See image below.

Additionally, an abstract has been published by SAGES (Society of Gastrointestinal Endoscopic Surgeons) in which a series of 3 patients has full-thickness esophageal reconstruction with a patch esophagoplasty using Gentrix with no stricture or clinically relevant leak followed out to one year (Nieponice, 2012).

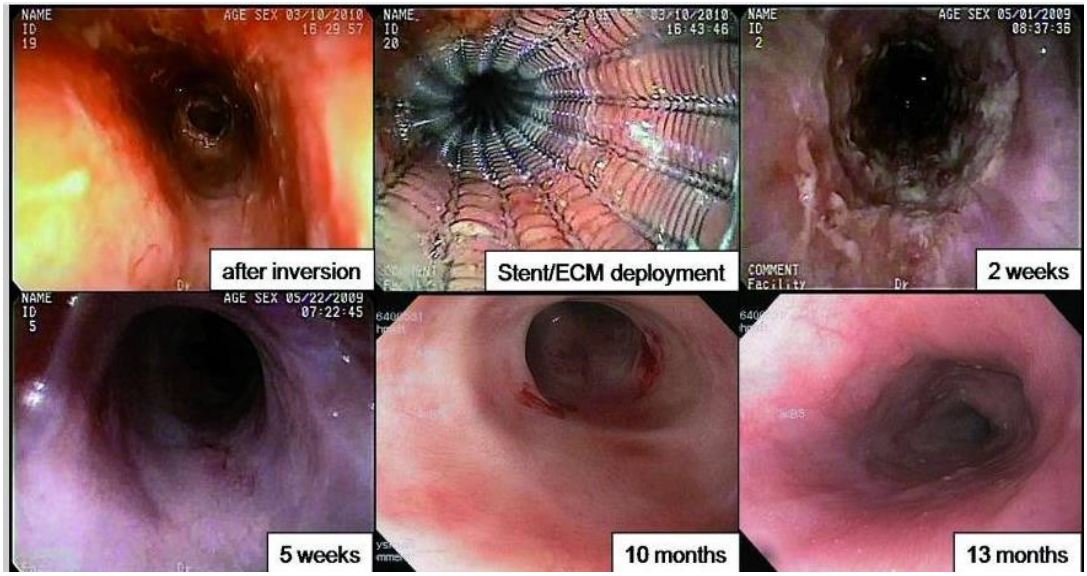


Image 5.1.1 – Badlyak et al. - representative endoscopic views of each stage in the procedure and follow-up.

ACell Gentrix Surgical Matrix PSM is a commercially available device that has been cleared for marketing by the FDA for implantation to reinforce soft tissue where weakness exists in urological, gynecological, and gastrointestinal anatomy including, but not limited to the following procedures: pubourethral support, tissue repair, body wall repair and esophageal repair.

5.3 Identification

ACell Gentrix Surgical Matrix PSM will be provided as product number PSM0412 which comes in one-time use 4 x 12cm strips.

5.4 Packaging and Labeling

ACell Inc. will provide the Gentrix PSM. Gentrix PSM is supplied E-Beam terminally sterilized in a double Tyvek pouch configuration all contained within an external box. Gentrix PSM will be provided as product number PSM0412 which comes in 4 x 12cm strips. Each subject will have one device implanted.

5.5 Storage, Handling, Disposal and Dispensing

Storage

Gentrix PSM is to be stored in a clean, dry environment at ambient temperature approximately 25^0C (77^0F) in unused and undamaged packages.

Handling and Disposal

The Gentrix PSM will be handled according to standard aseptic/sterile techniques.

Dispensing

The Gentrix PSM will be removed form the packaging according to standard aseptic/sterile technique. The material will be rehydrated in a sterile dish by submerging completely in room temperature sterile saline or sterile lactated Ringer's solution. The minimum rehydration time for Gentrix PSM is 15 minutes.

5.6 Initial Orders

MSK will maintain a minimum par level of two (2) Gentrix PSM devices and a maximum par level of eight (8) on the shelf at all times.

MDACC will maintain their own supply in accordance to their own independent contract with ACell

5.7 Re-Supply

Upon depletion of par levels to the minimum required quantity of two Gentrix PSM devices, MSK will re-order through standard MSKprocedures. All products will be directly shipped by ACell to MSK under standard ACell shipping procedures.

6.1 CRITERIAFOR SUBJECT ELIGIBILITY

Describe the characteristics of the patient/subject population.

6.2 Subject Inclusion Criteria

- Patient 18 years of age or older
- Pathologically confirmed Gastric, Gastroesophageal Junction (GEJ) or Esophageal, adenocarcinoma at either MSKCC or a participating site (biopsy may be performed at other institutions but slides must be confirmed at MSKCC or a participating site, as is routine care at our institution)
- Patient undergoing any resection requiring an anastomosis to the esophagus for curative intent. Including but not limited to esophagectomy or total gastrectomy.
- Subject is willing to provide written informed consent

- Subject is willing and able to comply with the follow-up regimen

6.3 Subject Exclusion Criteria

- Pregnant or lactating women
- Intraoperative evidence of metastatic or locally-unresectable disease
- Patients with known sensitivity or allergy to porcine materials.
- Patients undergoing any resection requiring an anastomosis to the esophagus for palliative intent.

7.0 RECRUITMENT PLAN

Patients from MSKCC will be recruited from the GMT and Thoracic surgical clinics at 53rd street, Dr. Yoon's GMT surgical clinic at Basking Ridge and Dr. Strong's clinic at West Harrison. Two thirds of all patients (approximatly 57) will come from the GMT clinics and one third of all patients (approximately 29) will come from the Thoracic clinics. Patients will also be enrolled at MDACC.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

This screening log of identifiable patient information will be kept in a password protected MSKCC registered database, CAISIS.

8.1 PRETREATMENT EVALUATION

- Signed Written Informed Consent
- Patients must be surgical candidates for esophageal anastomosis via TG, PG or Esophagectomy
- Relevant/Interval Medical History
- Physical examination
- Baseline Toxicity Evaluation
- Pre-Surgical Testing per Standard of Care of the site of device implementation.

9.1 TREATMENT/INTERVENTION PLAN

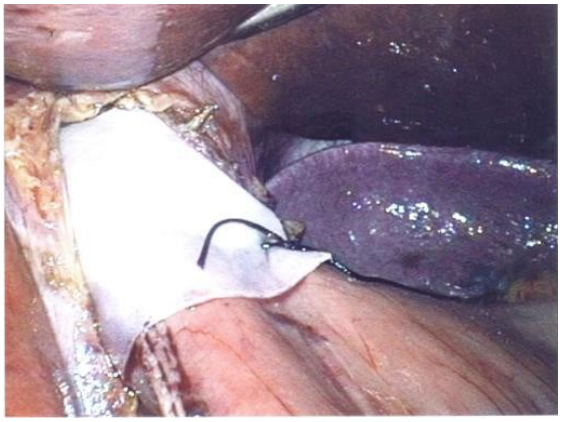
9.2 Management common to both groups

There are no restrictions on preoperative antibiotics, approach (laparoscopic or open), incision, and extent of lymph node dissection, margins, or other features of the

resection: the surgeon should proceed as he or she normally would in the absence of the trial. Most surgeons at MSKCC perform stapled gastrointestinal anastomoses but the type of primary anastomosis performed (stapled or hand-sewn) would be left to the discretion of the surgeon. Similarly, surgeons have the discretion to use nasogastric tubes or drains if they desire. Patients would undergo standard oncologic resection of their tumor by esophagectomy, PG or TG depending on site of disease. Patients with clinical evidence of advanced disease may undergo an initial laparoscopy procedure to evaluate for metastases prior to resection. Patients found to have metastatic disease would not undergo resection and would not be eligible for the study. Up to this point in the treatment course, all procedures would have been routine.

9.3 Anastomotic reinforcement with ACell Gentrix PSM

All esophageal anastomoses will be reinforced circumferentially with ACell Gentrix PSM. The material will be secured with ~ 2 cm overlap of the material proximal and distal to the anastomosis (see below).



ACell Gentrix PSM shown wrapped circumferentially around an esophagojejunal anastomosis with anchoring stitch after total gastrectomy reconstruction.

After anastomotic reinforcement, the procedure will be completed in a routine fashion with final assessments for hemostasis, drain placement when indicated, and wound closure.

9.4 Postoperative care

Most inpatient postoperative management decisions will be left to the discretion of the surgeon, including intravenous hydration, removal of nasogastric tubes or drains, initiation of diet, investigations, management of complications, and discharge. Post-operative length of stay will be as per routine of the surgeon. All patients undergoing esophagogastric resection will have a contrast swallow evaluation on post-operative day #4-10 to assess for radiographic evidence of anastomotic leak.

Outpatient management will entail postoperative follow up visits at 21 days (+/- 7 days), and at 90 days (+/- 14 days). If during the follow up period, patients report any symptoms suggestive of anastomotic stricture, a contrast study (esophagram) or endoscopy will be obtained at that time to evaluate for stricture. These tests will be performed as per standard postoperative assessment by the surgeon.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

Clinical assessment for anastomotic leak will be carried out during the course of the hospitalization after surgery and up to 90 days +/-14 days postoperatively. One radiographic assessment for leak will be performed during the interval from postoperative day 4-10. The grade of leak will be assigned according to standard criteria. For patients who die in the first 120 days following surgery where no documentation of leak has occurred, a request for autopsy will be made to determine the cause of death and will clarify whether or not a leak had occurred.

Clinical assessment for stricture will take place at 90 days +/- 14 days postoperatively. Patients will be evaluated in the outpatient clinic and will be assigned a dysphagia score from 0-4 by the RSA or clinical staff based on the following scale:

- 0 – Able to eat a normal diet
- 1 – Able to eat some solid food
- 2 – Able to eat semisolids only
- 3 – Able to swallow liquids only
- 4 – Unable to swallow anything

A dysphagia score of >/= 2 will prompt further work up with upper endoscopy and possible dilatation if stricture is identified.

Patients may also be called by a member of the research team check on their health status until the study closes. This will allow for more robust data to be collected on the long term affects of the Gentrix implantation.

Data for cost metrics will be collected postoperatively through POD90 (+/- 14 days). These include metrics such as Length of Stay, Readmission, Complications, Reoperation and Total Hospital Bill. Total hospital bill data will be obtained from the Physician Billing Department. Data will be collected for all 86 patients enrolled and summarized. Cost of total hospital bill will be determined from the date of admission on protocol to day of discharge on protocol. Additional cost of re-admission to day of discharge of re-admission will so be included.

Examination/Intervention	**Preop Visit(s)**	**OR**	**POD 4-10**	**POD21 (+/- 7 days)**	**POD90 (+/- 14 days)**	**Every 3 months until the study closes**
Obtain Informed Consent	X					
Relevant / Interim Medical History	X			X	X	
Physical Exam	X					
Pre Surgical Testing	X					
Surgery		X				
Implantation of Gentrix PSM		X				
Thin-barium or Gastrografin Swallow Evaluation			X			

Dysphagia Score					X	
Symptom Assessment				X	X	
AE Assessment	X			X	X	
Review of the patient's medical record						X

*Note: A member of the research team may contact the patient via telephone until the study closes. This phone call will assess the patient's well being after surgery.

Table 10.1 – Assessments and investigations during the course of the trial. An "X" denotes an assessment or test that all patients will undergo.

11.0 TOXICITIES/SIDE EFFECTS

Esophagectomy, PG and TG are substantial operations with associated morbidity including anastomotic leak, stricture, and bleeding. All patients undergoing esophagectomy, PG or TG are at risk of these events irrespective of entry into the trial. The most common complications include anastomotic leak, bleeding, wound infection, anastomotic stricture, and bowel obstruction. We do not anticipate increased toxicity or side effects as a result of anastomotic reinforcement with Gentrix PSM. However we will carefully evaluate for and document any potential adverse events such as infection, chronic inflammation, fistula formation, seroma formation, hematoma, recurrence of tissue defect, allergic reaction, and fever or chills as is our standard protocol.

Postoperative toxicities will be graded on a scale of 0 to 5 as described by the NCI-Common Terminology for Adverse Events (CTCAE) version 4.0.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary outcome of the trial is the rate of anastomotic leak after reinforcement of esophageal anastomoses with Gentrix PSM. Esophageal anastomotic leaks will be determined by one routine postoperative contrast swallow study on 4-10 as well as clinical course. Anastomotic stricture formation occurs later in the postoperative period and will be diagnosed based on symptomatology. Patients reporting symptoms consistent with stricture will be evaluated with radiographic contrast swallow study or endoscopy.

13.0 CRITERIA FOR REMOVAL FROM STUDY

The intervention in this trial is an isolated event (surgery), with routine post-operative care. Thus, there are no criteria to remove patients from the trial other than patient withdrawal of consent or death. Patients are permitted to withdraw consent at any time if they desire and will not undergo further trial investigations if they do so. Patients will be made aware that they cannot have the Gentrix PSM removed once it is implanted.

14.0 BIOSTATISTICS

The historical control leak rate at our institution among patients receiving partial, total gastrectomy or esophagectomy is 8-15%: esophagectomy leak rate of around 15% and total and proximal gastrectomy leak rate of around 10%. A weighted average of 13% between the groups will be considered an unacceptable leak rate. We will employ Simon's two stage design to show a decrease in the leak rate assessed radiographically and clinically from 13% to 5% which would require 86 total patients to detect this difference with type I and II error rates of 10% each. In the first stage we will enroll 43 patients and if 5 patients experience a leak, then the study will be terminated, however if only 4 or less patients experience a leak then we will proceed to accruing up to 86 patients. If at the end of the second stage we see 7 or less leaks then we will consider the study worthy of further investigation. We expect two thirds of the accrued patients to have total gastrectomy performed while the rest to receive esophagectomy. Exact 95% confidence intervals will be computed for the leak rate for all the patients as well as separately for esophagectomy and total gastrectomy.

Similarly, the stricture rate will be estimated using binomial proportions and exact 95% CI will be computed.

The different cost metrics will be summarized descriptively: continuous cost metrics will be summarized using medians and ranges while binary variables will be summarized using binomial proportions.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.3 Randomization

N/A

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting,

regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team.

The data collected for this study will be entered into an institutionally registered database. Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Monthly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb2.mskcc.org/irb/index.htm

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board. During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which will conform to MSKCC IRB guidelines.

1. Risks to the Subjects

Human Subjects Involvement and Characteristics: All patients at MSKCC who meet the inclusion criteria will be eligible. 86 patients will be entered on the trial; patients will be 18 years of age or older. Both men and women and members of all ethnic groups are eligible for this trial. This protocol does not include children because the number of otherwise eligible children is expected to be low. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

2. Adequacy of protection against risks

Consent process:

All patients at MSKCC and participating sites who meet the inclusion criteria will be eligible. Participation in the trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to institutional IRB guidelines. Per MSKCC Policy, an IRB approved Consenting Professional listed on the face page of this trial will conduct the consent discussion with the patient and obtain written informed consent. The informed consent procedure is described in Section 18.

Possible Toxicities/Adverse Effects:

There are no known additional risks of Gentrix devices as described in Section 11.0.

Costs:

Gentrix PSM will be provided to Memorial Sloan-Kettering by ACell. Patients will not receive any compensation for participation in the study. In addition, subjects will not incur any additional costs as a result of participation in the study.

Alternatives:

The alternative to this trial is to have surgery without use of the Gentrix PSM, or have no surgery.

Confidentiality:

Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate personnel (e.g. qualified monitors from MSKCC) may review patient records as required.

Patient safety:

Patients are monitored by physicians and nurses during the post-operative period. In the case of an adverse reaction, immediate medical attention is available. In the evenings and weekends, we have a 24-hour urgent care facility, for outpatients. The PI will also be available at all times to organize any necessary intervention.

Monitoring of data to ensure safety:

This study will be monitored according to MSKCC and Department of Surgery Policies by the institutional IRB. The analysis of safety will include patient case review and

regulatory binder review. Adverse events, including all toxic effects of treatment, will be tabulated individually and summarized by severity and causality.

3.Potential benefits of the proposed research to the subjects and others

This trial aims to lower the leak and stricture rate in patients undergoing esophagectomy and Total Gastrectomy patients. Initial pilot data here at MSKCC suggests that there is a benefit of reinforcing the anastomosis with Gentrix PSM.

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in 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
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- If an amendment will need to be made to the protocol and/or consent form
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition

Indication if the subject remains on the studyThe PI's signature and the date it was signed are required on the completed report.

17.2.1 ACell SAE Reporting

SAE Reporting

For non-MSKCC sites, all SAEs will be first reported to MSKCC.
Following reporting of SAEs to MSKCC, MSKCC will then report all SAEs to ACell.

ACell Quality Assurance (Phone: 410-953-8524, Fax: 410-715-4511, larrygroves@acell.com, scottcampanella@acell.com) is to be notified of **any** serious device-related adverse event within 24 hours of the Investigator's awareness of the event.

Relationship of AEs

For any adverse event recorded/described, the Investigator shall indicate, to the best of his/her knowledge, an assessment of the relationships between the AE and device and between the AE and procedures according to the following definitions:

Relationship to Device

- Unrelated: There is no relationship between the AE and the investigational device product. This may include but is not limited to the incident being an expected outcome of a previously existing or concurrent disease, concomitant medication or procedure the subject experienced.

- Possible: There is no clear relationship between the AE and the study device; however, one cannot definitely conclude that there is no relationship.

- Probable: While a clear relationship to the device under investigation cannot be established, the AE is associated with an expected AE or there is no other medical condition or intervention, which could explain the occurrence of such an event.

- Definite: The relationship of the AE and the study device can definitely be established.

Relationship to Procedures

- Unrelated: There is no relationship between the AE and the procedure. This may include but is not limited to the incident being an expected outcome of a previously existing or concurrent disease, concomitant medication or procedure the subject experienced.

- Possible: There is no clear relationship between the AE and the procedure; however, one cannot definitely conclude that there is no relationship.

- Probable: While a clear relationship to the procedure cannot be established, the AE is associated with an expected AE or there is no other medical condition or intervention, which could explain the occurrence of such an event.

- Definite: The relationship of the AE and the procedure can definitely be established.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix 1. Courtesy of Dr. Nabil Rizk

Hospital charges on 6 random esophagectomies +/- a leak

Leak: $82,815, $109,229, $550,612, $96,470, $113,112, $73,853

No Leak: $55,863, $44, 535, $48,425, $91,715, $77,573, $59,553