A Prospective Post-Market Clinical Evaluation of Miromatrix Biological Mesh for Hiatal Hernia Repair (MIROMESH PM-2)

Protocol Number 2015002

Version B
June 5, 2015

Miromatrix Medical Inc.
10399 West 70th Street
Eden Prairie, MN 55344

Approvals

Name and Title	Signature	Date
Robert Cohen, President & CEO		
Jeff Ross, Ph.D., VP of Product Development		
Angela Sullivan, Clinical Trials Manager		

MIROMATRIX MEDICAL
Clinical Research Protocol

A PROSPECTIVE POST-MARKET CLINICAL EVALUATION OF MIROMATRIX BIOLOGICAL MESH FOR HIATAL HERNIA REPAIR ("MIROMESH PM-2")

Protocol Number:	2015002
Version Date:	June 5, 2015
Device:	Miromatrix Biologic Mesh (MIROMESH®)
Study Phase:	Post Market
Sponsor:	Miromatrix Medical Inc. 10399 West 70th Street Eden Prairie, MN 55344
National Principal Investigator:	Michael Rosen, MD

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LIST OF ABBREVIATIONS

AE	Adverse Event
ASA	American Society of Anesthesiology
CFR	Code of Federal Regulations
CRF	Case Report Form
EGD	Esophagogastroduodenoscopy
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEJ	Gastroesophageal Junction
GERD-HRQL	Gastroesophageal Reflux Disease Health-Related Quality-Of-Life
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MDR	Medical Device Reporting
PI	Principal Investigator
QC	Quality Control
QOL	Quality of Life
SF-36®	The Short-Form (36) Health Survey
SF-36v2™	The newest version of the SF-36
Survey Materials	SF-36 Licensed Surveys, Software, SMS Scoring Solution, and all intellectual property rights related thereto
UGI	Upper Gastrointestinal Imaging

PROTOCOL SYNOPSIS

TITLE	A Prospective Post-Market Clinical Evaluation of Miromatrix Biological Mesh for Hiatal Hernia Repair
SHORT TITLE	MIROMESH PM-2
SPONSOR	Miromatrix Medical Inc.
NUMBER OF SITES	Up to 6
RATIONALE	This study is being conducted to gather long-term data of the performance of the Miromatrix Biological Mesh.
STUDY DESIGN	This is a post-market, interventional, prospective, single arm, multi-site study.
PRIMARY OBJECTIVE	The primary objective is to summarize freedom from hernia recurrence requiring reoperation at two years post procedure.
SECONDARY OBJECTIVES	The secondary objectives are to: • Summarize freedom from hernia recurrence requiring reoperation at one year post procedure • Summarize quality of life and freedom from symptomatic hernia recurrence over time • Summarize freedom from hernia recurrence as seen on radiographic imaging over time • Summarize device-related and procedure-related adverse events over time • Summarize procedure characteristics for the hiatal hernia repair surgery
PRIMARY ENDPOINT	The primary endpoint is an assessment of hernia recurrence requiring surgical reoperation at two years year post procedure for subjects that received implant of the mesh.
SECONDARY ENDPOINTS	• Assessment of hernia recurrence requiring surgical reoperation at one year post procedure for subjects that received implant of the mesh • Assessment of quality of life and symptomatic hernia recurrence using the SF-36, GERD-HRQL, and symptom questionnaires at baseline, 2 weeks, 2 months, 6 months, 1 year, 18 months, and 2 years • Assessment of hernia recurrence >2 cm as seen on radiographic imaging at one year and two years post procedure in comparison to discharge imaging. • Assessment of device-related and procedure-related adverse events over time • Procedure characteristics for the hiatal hernia repair surgery will include at a minimum: – Length of hospital stay – Procedure time – Implant success
NUMBER OF SUBJECTS	Up to 50 subjects will be enrolled in this study.

INCLUSION CRITERIA	To be considered for study participation, prospective subjects must: • be between 18 and 80 years old on the day of study enrollment • be able and willing to sign the consent form and comply with all study visits and procedures • be able to undergo elective laparoscopic hiatal hernia repair • be free of cognitive or speech impairment • have a documented, symptomatic type II or III hernia ≥5cm in the axial/vertical dimension • commit to non-smoking for at least 4 weeks prior to procedure
EXCLUSION CRITERIA	To be considered for study participation, prospective subjects must NOT: • have had a previous operation of the esophagus or stomach • have a sensitivity to porcine material • be pregnant or plan to be pregnant within next 2 years • be immunocompromised or at risk of immunosuppression (i.e. be HIV positive, be experiencing organ rejection, be a recent or anticipated chemotherapy recipient) as determined by the Investigator • require emergent operation for acute gastric volvulus or strangulation • be American Society of Anesthesiology (ASA) class 4 or greater • have a BMI ≥40 • have a life expectancy of less than 2 years at the time of enrollment • have an associated gastrointestinal disease that requires extensive medical or surgical intervention that might interfere with the quality of life assessment (e.g. Crohn's disease) • have any condition in the opinion of the Investigator that would preclude the use of the study device, or preclude the subject from completing the follow-up requirements
INTENDED USE OF STUDY DEVICE	The Miromatrix Biologic Mesh is intended to be implanted to reinforce soft tissue.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be enrolled in the study for up to 2 years (± 30 days) **Screening:** up to 60 days **Treatment:** 1 day (surgical procedure) **Follow-up:** Discharge, 2 week, 2 month, 6 month, 1 year, 18 month, and 2 year
EVALUATIONS	X-ray series with barium swallow (UGI) SF-36 Quality of Life (QOL) Survey GERD-HRQL Questionnaire Symptom Visual Analog Scales (VAS)

STATISTICS **Primary Analysis Plan**	This trial is descriptive in nature with no pre-specified hypothesis. Continuous data will be summarized using means, standard deviations, medians, ranges, and possibly 95% confidence intervals. In addition, where assessments are made over time, the differences from baseline may be statistically tested to see if different from zero using paired Student's t-test for parametric data or Wilcoxon Signed Rank test if non-parametric data. An alpha of 0.05 will be considered statistically significant and no adjustments for multiple testing will be made. Categorical data will be presented as counts and percentages.
Rationale for Number of Subjects	Up to 50 subjects will be enrolled to provide data of hernia recurrence at two years post procedure in addition to long-term symptomatic and asymptomatic hernia recurrence and quality of life. There is not a pre-specified sample size calculation, but a sample size of 30 is "rule of thumb" generally accepted as an adequate sample size for human studies. (1)

1.0 PURPOSE OF THE INVESTIGATION

1.1. Background

Surgical mesh used for hernia repair is classified by the FDA as a Class II medical device, which means that new surgical meshes receive "clearance" for marketing via the 510(k) process. In order for a new surgical mesh to receive clearance, it is required to demonstrate substantial equivalence to a predicate device. The process is designed to assure safety and efficacy of new Class II devices without requiring over-burdensome clinical data. It fosters the advancement of technology and allows new manufacturers to enter the marketplace in an expeditious fashion without introducing unreasonable risk to the public. Because clinical data is not required for a company to receive 510(k) clearance of a device, and because clinical trials can be extremely costly, there is a scarcity of prospective safety and efficacy-driven trials for new surgical meshes. The relative lack of clinical data for the many types of surgical mesh on the market today can make it difficult for surgeons to select the best mesh for a given procedure.

Hiatal hernia repair may be done with or without the use of mesh; however, the SAGES Guidelines Committee states that "the use of mesh reinforcement of large hiatal hernia repairs leads to decreased short term recurrence rates" (2). The Committee also identifies a need for longer-term results. Extending the focus from large hiatal hernias to small ones, Schmidt et al. performed a retrospective review of 70 patients with 1-5 cm hiatal hernias and reported a recurrence rate of 16% (5/32) in the suture cruroplasty group, compared with a recurrence rate of 0% (0/38) in the group with crural reinforcement with absorbable mesh (3). Their research points to the value of using biologic mesh in even small hiatal hernia repairs.

Despite ongoing concerns related to the use of synthetic mesh in hiatal hernia repair including erosion, dysphagia, and stricture, Wassenaar et.al. studied 73 subjects who had laparoscopic hiatal hernia repair with biologic mesh, with a median follow-up time of 45 months totaling 530 patient years, and found no evidence of stricture, ulceration, or erosion in any of the patients. Given the absence of major complications and the high (>90%) overall satisfaction with the operation, this research underscores the value of biologic mesh for hiatal hernia repair (4).

Miromatrix Medical has developed MIROMESH® - a new, noncrosslinked, acellular mesh derived from the highly vascularized porcine liver. MIROMESH received FDA 510(k) clearance with an indication for reinforcement of soft tissue on March 31, 2014 under K134033. The company believes that this biological mesh is superior to other biological meshes on the market due to the unique sourcing and processing of the material. The perfusion decellularization technique used to create the product is the only technology available to fully decellularize solid organs while maintaining their structure and vasculature, thereby allowing production of a highly vascularized, full-thickness biological mesh for hernia repair. The substantial vascularity and favorable tissue composition of this biological mesh differentiate it from the thin, dense (primarily skin) tissues currently on the market that rely on immersion decellularization.

This study will serve to provide clinicians with high-quality clinical data in order to provide them with a higher degree of confidence when selecting MIROMESH for hiatal hernia repair.

1.2. Name of study device
The study device is Miromatrix Biological Mesh (MIROMESH®).

1.3. Description of study device
Miromatrix Biologic Mesh is an FDA-cleared medical device. It is a noncrosslinked acellular surgical mesh that is derived from the highly vascularized porcine liver and is processed and stored in a phosphate buffered aqueous solution. Miromatrix Biologic Mesh is packaged in an inner sterile pouch and outer non-sterile pouch.

1.4. Intended use of the study device
The Miromatrix Biological Mesh is intended to be implanted to reinforce soft tissue.

1.5. Objectives of the clinical investigation

1.5.1. Primary objective
The primary objective is to summarize freedom from hernia recurrence requiring operation at two years post procedure.

1.5.2. Secondary objective(s)
The secondary objectives are to:

- Summarize freedom from hernia recurrence requiring reoperation at one year post procedure
- Summarize quality of life and freedom from symptomatic hernia recurrence over time
- Summarize freedom from hernia recurrence as seen on radiographic imaging over time
- Summarize device-related and procedure-related adverse events over time
- Summarize procedure characteristics for the hiatal hernia repair surgery

1.6. Anticipated duration of the clinical investigation
The anticipated duration of the clinical duration is 30 months. This duration covers enrollment of the first study subject to 2-year follow-up of the last study subject.

2.0 CLINICAL PROTOCOL

2.1 Protocol number and title
2015002: A Prospective Post-Market Clinical Evaluation of Miromatrix Biological Mesh for Hiatal Hernia Repair (MIROMESH PM-2)

2.2 Protocol version number and date
Version B, June 5, 2015

2.3 Study design
This is a post-market, interventional, prospective, single arm, multi-site study.

2.4 Subject selection

2.4.1 General characteristics of the proposed subject population(s)

The proposed subject population includes males and females between 18 and 80 years of age who are candidates for repair of a hiatal hernia with surgical mesh.

2.4.2 Anticipated number of research subjects

Up to 50 subjects will be enrolled in the study. Enrollment is defined as the point at which the prospective subject signs the IRB-approved consent form, however only subjects that are enrolled AND have an implant attempted will count toward the sample size. A sample size of 30 is "rule of thumb" generally accepted as an adequate sample size for preliminary summaries. Assuming 100% implant success and a 10% 2-year attrition rate, at least 27 subjects are expected to complete the study.

2.4.3 Inclusion criteria

To be considered for study participation, prospective subjects must:

- be between 18 and 80 years old on the day of study enrollment
- be able and willing to sign the consent form and comply with all study visits and procedures
- be able to undergo elective laparoscopic hiatal hernia repair
- be free of cognitive or speech impairment
- have a documented, symptomatic type II or III hernia ≥5cm in the axial/vertical dimension
- commit to non-smoking for at least 4 weeks prior to procedure

2.4.4 Exclusion criteria

To be considered for study participation, prospective subjects must NOT:

- have had a previous operation of the esophagus or stomach
- have a sensitivity to porcine material
- be pregnant or plan to be pregnant within next 2 years
- be immunocompromised or at risk of immunosuppression (i.e. be HIV positive, be experiencing organ rejection, be a recent or anticipated chemotherapy recipient) as determined by the Investigator
- require emergent operation for acute gastric volvulus or strangulation
- be American Society of Anesthesiology (ASA) class 4 or greater
- have a BMI ≥40
- have a life expectancy of less than 2 years at the time of enrollment
- have an associated gastrointestinal disease that requires extensive medical or surgical intervention that might interfere with the quality of life assessment (e.g. Crohn's disease)
- have any condition in the opinion of the Investigator that would preclude the use of the study device, or preclude the subject from completing the follow-up requirements

2.5 Study procedures

2.5.1 Screening and consenting procedures

Patients who are candidates for laparoscopic hiatal hernia repair will be considered for study participation. Trained site personnel will review prospective study subject charts to rule out any obvious study exclusion criteria prior to introducing the study to the patient.

Prior to the hernia repair surgery, the Principal Investigator (or a trained and qualified delegate) will introduce the study and review the full set of study criteria with the patient. If the patient meets all study criteria, the PI or delegate will review the current IRB-approved consent form with the patient. The patient will be encouraged to ask questions and will have all of their questions addressed to their satisfaction before deciding whether or not to be in the study. A copy of the consent form will be made available to the subject to take home for review and discussion with family members. If the patient agrees to participate in the study, (s)he will sign the consent form and will be provided with a signed copy for their records. Upon signing the consent form, the patient will be considered "enrolled" as a study subject. Refer to section 6.0 for additional details about the consent process.

2.5.2 Surgical treatment

Antibiotics will be administered prophylactically according to the physician's standard practice.

All study subjects will receive the FDA cleared MIROMESH study device as part of their laparoscopic hiatal hernia repair surgery. Prior to use, the study device(s) will be soaked for a minimum of 2 minutes using a sterile basin and room temperature sterile saline or room temperature sterile lactated Ringer's solution to cover the mesh.

The hernia sac should be dissected away from mediastinal structures and excised whenever possible. The gastroesophageal junction (GEJ) will be returned to a tension-free infradiaphragmatic position with the intra-abdominal esophagus measuring at least 2 cm. Collis gastroplasty, as well as gastropexy, will be documented for study records if performed.

The crura will be closed with interrupted sutures whenever possible. MIROMESH should be trimmed in a way to accommodate the specific subject's anatomy and defect, and should then be placed in an onlay fashion to reinforce primary crural closure. A small space of at least 0.5 cm should be left between the edge of the mesh and the esophageal wall to avoid excessive contact of the mesh with the esophagus (4) (5). Mesh fixation may be achieved with glue, tacks, or sutures, or any combination thereof. Care should be taken that fixation methods do not breach the aorta or pericardium when applied low on the left crus or near the apex of the crura anteriorly (2). Fundoplication will be performed at the discretion of the investigator and the degree of wrap will be documented for study records.

Subjects should not be placed on the immunosuppressant drug rapamycin for at least 30 days post-surgery, as it has been shown to inhibit vascularization and incorporation of surgical mesh (6).

2.5.3 Study visits

Table 1. Schedule of Study Visit Activities

Activity	Study Visit									
	Enrollment	Baseline (within 60 days of Procedure)	Procedure	Discharge (may be 1 day prior)	Follow-Up Time Period from Surgery					
					2 Week (±7 days)	2 Month (± 15 days)	6 Month* (± 30 days)	1 Year (± 30 days)	18 Month* (± 30 days)	2 Year (± 30 days)
Review study criteria	X									
Medical History		X								
Physical Exam		X		X	X	X		X		X
SF-36 QOL Survey		X			X	X	X	X	X	X
GERD-HRQL and Symptoms Survey		X			X	X	X	X	X	X
UGI X-ray with barium				X				X		X
Assess Adverse Events		X	X	X	X	X	X	X	X	X

* The 6-Month and 18-Month Visits may be conducted remotely via telephone, email, and/or mail.

Table 2. Schedule of Study Visit Case Report Forms

CRF Name	Study Visit									
	Enrollment	Baseline (within 60 days of Procedure)	Procedure	Discharge (may be 1 day prior)	Follow-Up Time Period from Surgery					
					2 Week (±7 days)	2 Month (± 15 days)	6 Month* (± 30 days)	1 Year (± 30 days)	18 Month* (± 30 days)	2 Year (± 30 days)
Enrollment	X									
Baseline		X								
Procedure			X							
Follow-Up				X	X	X		X		X
SF-36		X			X	X	X	X	X	X
Symptoms**		X			X	X	X	X	X	X
Protocol Deviation	As Applicable									
Adverse Event	As Applicable									
Re-intervention	As Applicable									
Discontinuation	As Applicable (must complete one per subject)									

* The 6-Month and 18-Month Visits may be conducted remotely via telephone, email, and/or mail.
**The Symptoms CRF includes the GERD-HRQL survey as well as symptom Visual Analog Scales

At the **Enrollment Visit**, study inclusion and exclusion criteria will be reviewed. If the patient meets all inclusion criteria and none of the exclusion criteria and wishes to participate in the study after careful consideration, they will be asked to sign the consent form. The patient is considered to be enrolled as a study subject upon signing the consent form.

At the **Baseline Visit**, the subject's demographics, medical history, and hernia information will be reviewed and recorded on the Baseline CRF. The subject will be asked to complete the SF-36 QOL and Symptoms CRF. This visit should be conducted within sixty (60) days prior to the procedure.

At the **Procedure Visit**, the subject will be undergo laparoscopic hiatal hernia repair according to section 2.5.2 above. Procedural details to be collected on the Procedure CRF include: surgery duration, operative approach and technique, hernia sac dissection and excision, mesh trimming and placement, fundoplication degree, gastropexy, gastroplasty, fixation information, hernia size, device size and lot number.

At the **Discharge Visit**, physical exam information will be recorded on the Follow-Up CRF and the subject will have a UGI x-ray with barium contrast. The discharge visit may be conducted 1 day prior to discharge.

At the **2-Week Visit and 2-Month Visit**, physical exam information will be recorded on the Follow-Up CRF. The subject will be asked to complete the SF-36 QOL and Symptoms CRF. The 2-week visit allows for a ±7 day window. The 2-month visit allows for a ±15 day window.

The **6-Month Visit** may be conducted remotely via telephone, email, and/or mail. The subject will be asked to complete the SF-36 QOL and Symptoms CRF, both which should be administered in a manner that is convenient to the subject. The subject should also be asked specifically about reportable adverse events. The 6-month visit allows for a ±30 day window.

At the **1-Year Visit**, physical exam information will be recorded on the Follow-Up CRF and the subject will have a UGI x-ray with barium contrast. The subject will be asked to complete the SF-36 QOL and Symptoms CRF. The 1-Year visit allows for a ±30-day window.

The **18-Month Visit** may be conducted remotely via telephone, email, and/or mail. The subject will be asked to complete the SF-36 QOL and Symptoms CRF, both which should be administered in a manner that is convenient to the subject. The subject should also be asked specifically about reportable adverse events. The 18-month visit allows for a ±30 day window.

At the **2-Year Visit**, physical exam information will be recorded on the Follow-Up CRF and the subject will have a UGI x-ray with barium contrast. The subject will be asked to complete the SF-36 QOL and Symptoms CRF. The 2-Year visit allows for a ±30-day window.

Protocol deviations and adverse events will be documented, recorded, and promptly reported from the time of study enrollment through study discontinuation. A Discontinuation CRF will be completed upon the subject's 2-year study visit, or sooner if necessary.

2.5.4 Subject Surveys

Miromatrix Medical Inc. has entered into an agreement with OptumInsight Life Sciences, Inc. to use the SF-36v2™ survey for this study. SF-36v2™ is a 36-question quality-of-life survey that is commonly used in research, including hernia studies. It measures eight domains; four of these are related to physical heath, and four are related to mental health. The physical health domains include physical functioning, physical role, bodily pain, and general health. The mental health domains include vitality, social functioning, emotional role, and mental health. Investigators may use and administer the Survey Materials only through investigational sites, only on behalf of Miromatrix Medical Inc., only during the Study Term (June 11, 2015 to March 31, 2018) and only for the Approved Purpose (MIROMESH PM-2). Investigator sites may not use the Survey Materials for any other purpose. Refer to Appendix C for additional details.

The GERD Health Related Quality of Life (GERD-HRQL) survey will serve as a measurement tool for this study due to the close relationship between hiatal hernia and gastroesophageal reflux disease (GERD) symptoms. The survey provides a quantitative method of measuring GERD symptom severity. There are 51 possible scores, imparting the instrument with a high level of precision; and because of the response anchors, the instrument cannot have a floor effect. A study by Velanovich also implies little ceiling effect. The GERD-HRQL has been shown to be reliable, valid, and practical for the assessment of symptom severity in gastroesophageal reflux disease (7).

In addition to the GERD-HRQL survey, subjects will be asked to complete symptom Visual Analog Scales (VAS) to assess the following hernia-related symptoms: regurgitation, chest pain, abdominal pain, nausea, vomiting, postprandial pain, cardiovascular, and pulmonary. Subjects will be asked to indicate their symptoms over the previous 7 days by drawing a line on a 10-cm scale, with 0 representing ‘no effect on life’ and 10 representing ‘extreme effect on life’.

2.5.5 Hernia recurrence

Hernia recurrence is defined as a >2 cm protrusion of an organ through the esophageal opening in the diaphragm as identified on UGI (x-ray with barium contrast). This definition is consistent with the definition of hernia recurrence for a previous study (8). Recurrent hernias will be measured according to the distance from the apex of the hiatus to the posterior decussation of the left and right crus. Classification categories for reporting purposes will be as follows:

1) No evidence of recurrence
2) ≤2 cm organ protrusion above diaphragm
3) Between 2 and 4 cm organ protrusion above diaphragm
4) >4 cm organ protrusion above diaphragm

Asymptomatic recurrent hernias may not require reoperation but will still be reported on an Adverse Event CRF. In the event of study site hernia recurrence requiring surgical treatment, a Re-intervention CRF will be completed and the subject will be discontinued from the study.

2.5.5 Withdrawal of subjects due to non-compliance

A minimum of three contact attempts will be made to schedule subjects for follow-up visits, including at least one written attempt. After all attempts have been exhausted, a subject will be discontinued from the study.

2.5.6 Procedures to assess efficacy

As an FDA cleared Class II medical device, the study device is generally regarded as efficacious. The procedures conducted in this study may provide insight on the extent and/or rate of vascular in-growth of the biological mesh and clinical acceptance of the study device.

2.5.7 Procedures to assess safety

As an FDA cleared Class II medical device, the study device is generally regarded as safe. Device-related and procedure-related adverse events will be collected throughout the study and will be reported according to applicable regulations as outlined in section 3.2.

2.6 Study outcome evaluations

2.6.1 Study endpoints

The primary endpoint is an assessment of hernia recurrence requiring surgical operation at two years post procedure for subjects that received implant of the mesh. This assessment will be made at the 2-year follow-up visit. Additionally, any subjects that had surgical hernia re-intervention or the need for hernia re-intervention due to a recurrence according to the Adverse Event or Follow-Up CRF at any point in the previous two years post-procedure will be considered a failure.

Secondary endpoints:

- Assessment of hernia recurrence requiring surgical reoperation at one year post procedure for subjects that received implant of the mesh
- Assessment of quality of life and symptomatic hernia recurrence using the SF-36, GERD-HRQL, and symptom questionnaires at 2 weeks, 2 months, 6 months, 1 year, 18 months, and 2 years
- Assessment of hernia recurrence >2 cm as seen on radiographic imaging at one year and two years post procedure in comparison to discharge imaging.
- Assessment of device-related and procedure-related adverse events over time
- Procedure characteristics for the hiatal hernia repair surgery will include at a minimum:
  - Length of hospital stay
  - Procedure time
  - Implant success

2.6.2 Sample size determination

This trial is an observational trial designed to gather long-term data for assessing performance of the Miromatrix Biological Mesh (MIROMESH®). Up to 50 subjects will be enrolled to provide data of hernia recurrence at two years post procedure in additional to long-term assessments of subject symptoms and quality of life. There is no sample size calculation, but a sample size of 30 is “rule of thumb” generally accepted as an adequate sample size for preliminary summaries. While the exact rate of success (no recurrence of hernia requiring success) is unknown to this study population, Table 3 below provides expected 95% confidence interval widths for various sample sizes and success using the binomial approach. Using worst case scenario in the binomial distribution of 50%, the worst expected CI width will be in the 29-37% range with sample size of 30 to 50 subjects.

Table 3. Expected CI widths for the sample size and proportion of subjects free from hernia recurrence (binomial distribution, 2-sided alpha of 0.05).

Prop. Success	Sample Size				
	30	35	40	45	50
50% (WCS)	**37.4%**	**34.6%**	**32.4%**	**30.5%**	**28.9%**
85%	28.1%	25.9%	24.1%	22.7%	21.4%
86%	27.4%	25.3%	23.5%	22.1%	20.9%
87%	26.7%	24.6%	22.9%	21.5%	20.4%
88%	26.0%	23.9%	22.3%	20.9%	19.8%
89%	25.2%	23.2%	21.6%	20.3%	19.2%
90%	24.4%	22.4%	20.9%	19.6%	18.5%
91%	23.5%	21.6%	20.1%	18.8%	17.8%
92%	22.6%	20.7%	19.3%	18.0%	17.0%
93%	21.6%	19.8%	18.4%	17.2%	16.2%
94%	20.5%	18.8%	17.4%	16.2%	15.3%
95%	19.3%	17.6%	16.3%	15.2%	14.3%
96%	18.1%	16.4%	15.1%	14.1%	13.2%
97%	16.6%	15.1%	13.8%	12.8%	12.0%
98%	15.1%	13.5%	12.3%	11.4%	10.6%
99%	13.4%	11.8%	10.7%	9.7%	9.0%

2.6.3 Outcome data and data analysis

This trial is descriptive in nature with no pre-specified hypothesis. Continuous data will be summarized using means, standard deviations, medians, ranges and possibly 95% confidence intervals. In addition, where assessments are made over time, the differences from baseline may be statistically tested to see if different from zero using paired Student's t-test for parametric data or Wilcoxon Signed Rank test if non-parametric data. An alpha of 0.05 will be considered statistically significant and no adjustments for multiple testing will be made. Categorical data will be presented as counts and percentages.

Additionally, a Kaplan Meier survival analysis may be performed on the primary objective in case there are early withdrawals from the trial prior to the one year visit. Otherwise, a sensitivity analysis may be performed plugging in best and worst case scenario results using binomial techniques.

Summaries of the objectives will include all subjects with available data that received a MIROMESH implant and will include all assessments over time. Procedure characteristics may include all subjects that had a MIROMESH implant attempt.

Counts and incidences of adverse events will be summarized for all subjects with an implant attempted. Summaries may be presented by seriousness and/or relatedness to procedure/device.

2.6.4 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will be not used due to the post-market nature of the clinical study with a cleared device to be used in accordance with current labeling. Adverse events will be classified by investigators and will be reviewed by the study sponsor.

3.0 RISK ANALYSIS

3.1 Anticipated risks

The study involves an FDA cleared, class II device with greater than minimal risk to the subject. The greater than minimal risk designation (as defined in 45 CFR Part 46) is solely due to the x-ray imaging required at the discharge, 1-year, and 2-year visits. Some of this imaging (specifically the discharge x-ray) may be considered standard of care at certain facilities.

An x-ray of the upper GI tract provides an average radiation dose of 6 mSv. This amount of radiation is comparable to the natural background radiation for 2 years, with an additional lifetime risk of fatal cancer from the examination estimated at 1 in 10,000 to 1 in 1,000[1]. Subjects in this study will be exposed to three such doses, all approximately one year apart.

Anticipated risks of receiving the study device are the same regardless of whether a patient decides to participate in the study. Known risks related to surgical mesh for hiatal hernia repair include, but are not limited to (9):

- Infection
- Pain
- Adhesions
- Erosion/migration
- Compromised sterility
- Bleeding
- Mechanical failure
- Foreign body reaction
- Seroma
- No in-growth
- Mesh shrinkage
- Hematoma

There is a small risk of loss of confidentiality due to study participation.

3.2 Adverse event reporting

For the purposes of this study, reportable adverse events will be limited to all events related to, or possibly related to, the study device and/or procedure. There may be adverse events which meet the SAE definition but are not related to the device or procedure; such events will not be collected in this study. The sponsor will determine if an event meets Medical Device Reporting (MDR) requirements. All MDR reportable events will be reported to FDA as detailed in section 3.2.5.

3.2.1 Adverse event definitions

Adverse Event: Any untoward medical occurrence associated with the use of a device in humans, whether or not considered device related.

[1] http://www.radiologyinfo.org/en/safety/index.cfm?pg=sfty_xray

Adverse Device Effect: An adverse event caused by or related to the device.

Serious adverse effect: An adverse effect is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability or permanent damage
- a congenital anomaly/birth defect
- intervention to prevent permanent impairment or damage.

Life-threatening adverse effect: Any adverse effect that places the subject, in the view of either the investigator or the sponsor, at immediate risk of death from the effect **as it occurred**. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

MDR-reportable event: events that manufacturers become aware of that reasonably suggest that one of their marketed devices may have caused or contributed to a death or serious injury, or has malfunctioned and the malfunction of the device or a similar device that they market would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

3.2.2 Eliciting adverse effect information

Clinical study subjects will be routinely questioned about adverse events at study visits.

3.2.3 Recording and assessing of adverse effects

All observed or volunteered reportable adverse effects (serious or non-serious) will be recorded in the subjects' case histories. Sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a *serious adverse effect*) and; 2) an assessment of the casual relationship between the adverse effect and the study device.

Adverse effects believed to be associated with the study device will be followed until the effect (or its sequelae) resolves or stabilizes at a level acceptable to the investigator or until study completion, whichever is sooner.

3.2.4 Causality and severity assessment

The investigator will promptly review reportable adverse effects to determine 1) if there is a reasonable possibility that the adverse effect was caused by the study device or the study procedure; and 2) if the adverse effect meets the criteria for a *serious adverse effect*.

3.2.5 Reporting MDR reportable events to the FDA

The sponsor will electronically report MDR-reportable events to the FDA's Center for Devices and Radiological Health according to the table below.

Table 4. MDR Reporting Requirements

What to report	Reporting Timeframe
30 day reports of deaths, serious injuries and malfunctions	Within 30 calendar days of becoming aware of an event

What to report	Reporting Timeframe
5-day reports for an event designated by FDA or an event that requires remedial action to prevent an unreasonable risk of substantial harm to the public health	Within 5 work days of becoming aware of an event

Reports will consist of:

- a completed Form FDA 3500A
- a cover letter analyzing the significance of the event

A copy of the report will be provided to all participating study investigators.

Subsequent to the initial submission of a completed FDA Form 3500A, the sponsor will submit additional information concerning the reported adverse effect as requested by the FDA.

3.2.6 Reporting adverse effects to the responsible IRB

Reportable adverse events and follow-up information will be reported to the IRB according to the individual IRB's policies.

3.3 Withdrawal of subjects due to adverse effects

It is not expected that subjects will be withdrawn from the study due to adverse effects. In the event that a subject experiences an adverse effect which results in removal of the study device, the subject should continue study participation until resolution of the event. Upon resolution, the subject should be withdrawn from the study.

4.0 MONITORING PROCEDURES

Monitoring of the study for compliance with the clinical protocol and with applicable regulations will be conducted periodically by the sponsor and/or a designated CRO or equivalent.

The investigator and the institution will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify accuracy. In cases of institution policy which limit sponsor access to medical records, the institution will be required to provide adequate resources and procedures to ensure data quality and accuracy.

The study Monitoring Plan will be located in the sponsor's electronic study master file.

5.0 LABELING

The Instructions for Use document is located in Appendix A.

6.0 INFORMED CONSENT

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The sponsor will work with study site personnel to provide an informed consent form and HIPAA authorization to the IRB for approval. The written consent document will embody the elements of informed consent as described in CFR 21 CFR 50.25 and will also comply with local regulations. The Investigator will retain an IRB-approved copy of the Informed Consent Form in the study master file.

A properly executed, written, informed consent will be obtained from each subject prior to conducting any study-related procedures. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's study records at the site.

7.0 IRB INFORMATION

The protocol and consent form will be reviewed and approved by the IRB of each participating center prior to study initiation. Adverse events will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator and the Sponsor before the study is initiated. This approval must refer to the study by exact protocol title and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

8.0 ADDITIONAL RECORDS AND REPORTS

8.1 Data handling and record-keeping

Sample Case Report Forms (CRFs) are located in Appendix B. Paper CRFs will be used for this study and will be entered into a validated MS Excel spreadsheet using a 2-step process to ensure accuracy. At a minimum, an Enrollment CRF and a Discontinuation CRF will be completed for each subject enrolled into the clinical study. The investigator will review and sign each completed CRF; the investigator's signature serving as attestation of the investigator's responsibility for ensuring that all data entered on the CRF are complete, accurate and authentic.

Source Data are the clinical findings and observations, laboratory and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the *Source Data* recorded on the *Source Documents*.

Patient survey CRFs will be considered Source Documents when used as the original source (i.e. they are completed directly by the subject, or the subject's responses are recorded directly onto the CRF by site personnel).

8.2 Record maintenance and retention

The investigator will maintain the following study records:

- IRB correspondence (including approval notifications) related to the clinical protocol, including copies of adverse event reports and annual or interim reports
- All versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s)
- Signed Clinical Trial Agreement, Investigator's Agreements and Financial Disclosures
- Curriculum vitae for Investigators
- Training documentation for all study site personnel
- Signed informed consent forms
- Completed study worksheets (if used), signed and dated by investigator or delegated site personnel
- Source Documents or certified copies of Source Documents
- Monitoring visit communications
- Copies of sponsor notifications of adverse effect information

The sponsor will maintain the following study records:

- Copies of submitted Form FDA 3500A, notice of device recalls
- IRB correspondence (including approval notifications) related to the clinical protocol;
- All versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s)
- Signed Clinical Trial Agreement, Investigator's Agreements and Financial Disclosures
- Curriculum vitae for Investigators
- Training documentation for all study site personnel
- Monitoring visit reports and communications
- Corrective and Preventative Action (CAPA) Plans, if applicable
- Adverse effect communications to sites
- Final clinical study report

Subject study binders which include identifying information will be stored in a locked cabinet or office (or similar locked location) at the study sites. Subject confidentiality will be protected by the use of unique subject IDs in the electronic database (MS Excel spreadsheet). Subject identifying information will not be collected in the database. Additionally, subject names or other directly identifiable information will not appear on study reports, publications, or other disclosures of clinical study outcomes.

Investigators will retain the specified records and reports for a minimum of two years after the investigation has been discontinued. Investigators may seek sponsor approval to transfer custody of the records to any other person or entity who will accept responsibility for them.

9.0 PUBLICATIONS

9.1 Authorship

The study sponsor will be responsible for determining publication procedures and resolving authorship issues. Authorship may be determined by various means, including contribution to the study design and enrollment rate.

9.2 Trial Registration

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as *ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. The sponsor will register this trial on ClinicalTrials.gov in order for the research results to be considered for publication in ICMJE member journals.

References

1. *Breaking Free of Sample Size Dogma to Perform Innovative Translational Research.* **Bacchetti, Peter, Deeks, Steven G and McCune, Joseph M.** 2011, Science Translational Medicine, p. 87ps24.

2. *Guidelines for the management of hiatal hernia.* **Kohn, Geoffrey Paul, et al.** 27, New York : Springer Science+Business Media, 2013, Surgical Endoscopy, pp. 4409-4428.

3. *Hiatal hernia repair with biologic mesh reinforcement reduces recurrence rate.* **Schmidt, E, et al.** 27, Jan 2014, pp. 13-17.

4. *The safety of biologic mesh for laparoscopic repair of large, complicated hiatal hernia.* **Wassenaar, Eelco B., et al.** 26, 2012, Surgical Endoscopy and Other Interventional Techniques, pp. 1390-1396.

5. *The surgical treatment of paraesophageal hernias.* **Feo, Carlo V., Zuolo, Michele and Patti, Marco G.** 84, Ferrara, Italy : s.n., 2013, Annali Italiani di Chirurgia, pp. 257-262. Published online 29 October 2012.

6. *Rapamycin, but not cyclosporine A, inhibits vascularization and incorporation of implanted surgical meshes.* **Laschke, Matthias W., et al.** 6, 2009, Vol. 22, pp. 654-662.

7. *The development of the GERD-HRQL symptom severity instrument.* **Velanovich, V.** 20(2), 2007, Diseases of the Esophagus, pp. 130-4.

8. *Biological Prosthesis Reduces Recurrence After Laparoscopic Paraesophageal Hernia Repair.* **Oelschlager MD, Brant K., et al.** 4, s.l. : Annals of Surgery, October 2006, Vol. 244, pp. 481-490.

9. *Major mesh-related complications following hernia repair.* **Robinson, T.N., et al.** 2005, Surgical Endoscopy And Other Interventional Techniques, pp. 1556-1560.