STUDY PROTOCOL

"A Randomized, Prospective, Study Comparing Fortiva™ Porcine Dermis vs. Strattice™ Reconstructive Tissue Matrix in Patients Undergoing Complex Open Primary Ventral Hernia Repair"

Protocol: RTI-2015-02

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Ethics Statement: The study will be conducted according to the International Conference on Harmonization guideline E6 (R1): Good Clinical Practice: Consolidated Guideline.

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LIST OF ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
IEC	Independent Ethics Committee
FDA	Food & Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonization – Good Clinical Practice
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
PI	Primary Investigator
PDC	Porcine Derma Collagen
QOL	Quality of Life
SAE	Serious Adverse Event
VAS	Visual Analog Scale

I. Background

1.1 Introduction

In hernia repair, implants of various materials are often chosen as a means of reinforcing the tissue in the region of the herniation, and ensuring a greater likelihood of success, as measured by a lower incidence of recurrence. In primary closure, the recurrence rate has been cited as ranging from 24 to 66% [9,3,12] while the number has been reported as significantly lower when an implant was used for the repair.[11]

The use of implants in hernioplasties has been well documented and for this reason it is often a preferred procedure. One of the more common types of material for the prostheses used in hernioplasties is polypropylene implant, but the use of this material in contaminated fields is controversial. In complex hernias, such as large or small bowel resections, the surgical procedures are often potentially contaminating. Therefore, the use of certain materials such as polypropylene can be hazardous due to bacteria colonizing the mesh.[5] In addition, in the case of a large abdominal wall defect the use of a prosthetic device is mandatory, however it needs to be noted that it is not possible to use polypropylene in direct contact with bowel. [10,6]

When using an acellular dermal matrix derived from porcine in complex hernias, positive surgical results have been shown with no observed recurrences, while wound infections observed after a mean follow-up of 11.1 months showed no significant difference compared to primary closure. [1] Shaikh (2007) has also reported that recurrence rates for porcine acellular dermal matrix are similar to the recurrence rates when using synthetic materials. [13] A case study that used porcine acellular dermal matrix in a contaminated field, although limited in scope, has also shown positive surgical outcomes at one year post-surgery.[7] In an exposed bowel, Chuo, et al (2008) has demonstrated positive outcomes in patients with a variety of surgical situations including exposed bowel, contaminated abdominal wound beds and around stomas. [2] These outcomes certainly seem to support the animal models which have shown that biologic grafts, in comparison to synthetic material, are able to clear a Staphylococcus aureus contamination. [8]

Complex hernias include those that have either been repaired before on multiple occasions, those associated with infections, or those that have resulted in bowel perforations or fistulas. Porcine acellular dermal matrices (ADM) have recently been proposed as a means to offset the disadvantages of polypropylene synthetic implants, for example their inability to integrate into the patient's tissue thus creating a site for bacteria to colonize, and have since been used in humans for hernia repairs. While the polypropylene synthetic implants are permanent, the acellular dermal matrix implants have been shown to incorporate into the host, with the implanted tissue remodeling to resemble the original tissue, both histologically as well as functionally. The product we plan to use is a porcine acellular dermal matrix which will have been processed via the Tutoplast® Tissue Sterilization Process.

Animal models have been used extensively to assess implantable materials generally and implants of various materials for soft-tissue reinforcement in particular, despite significant limitations.2 A recent systematic review of biologic implants in animal studies concluded that supplemental cross-linking of collagen in tissue-based implants did not adversely affect the strength of the implant or its ability to support long-term ingrowth of native tissue.11 The limitations of animal models have, however, been clearly exposed recently by the comparison of the same two porcine dermal implants, Permacol™

(supplemental cross-linked; Covidien, New Haven, CT, USA) and Strattice™ Reconstructive Tissue Matrix (non-supplemental cross-linked; LifeCell Corporation, Bridgewater, NJ, USA), in different animal models, with startlingly differing results.12.13 Therefore, the extrapolation of results from animal data to the clinical context should be performed with caution. The choice of porcine acellular dermal matrices by the surgeon should be based on the evidence available from clinical studies pertinent to the context in which it is being used (www.ncbi.nlm.hih/gov/pmc/articles/PMC3956623/).

1.2 Rationale

Biologic materials such as Fortiva Porcine Dermis and Strattice Reconstructive Tissue Matrix were developed to provide reinforcement of hernia repair. However, limited high quality prospective data exists on the use of these materials in complex abdominal wall reconstruction, and no comparative data exists. Therefore the objective of this study is to compare the effectiveness of Fortiva Porcine Dermis versus Strattice Reconstructive Tissue Matrix for the underlay reinforcement of complicated ventral hernia repair and assess post-operative complication rates, long term hernia recurrence rates.

II. Study Design

This is a randomized, prospective, double-blinded study evaluating the efficacy of Fortiva Porcine Dermis versus Strattice Reconstructive Tissue Matrix in 120 patients with large complex abdominal wall ventral hernias undergoing single stage repair. The patient will be blinded to treatment as well as an independent qualified evaluator to confirm evidence of reoccurrence. This post-market study compares two FDA cleared biologic hernia materials. Fortiva™ porcine dermis, processed by RTI Surgical, Inc., a non-cross linked porcine dermis will be compared to Strattice™ Reconstructive Tissue Matrix by LifeCell, a non-cross linked porcine dermis for reinforcement during the single stage open reconstruction of abdominal wall defects. The primary outcome will be hernia recurrence at 1 year. Outcomes will be evaluated at 6 weeks, 3 months, 6 months and 12 months and 24 months.

21 CFR 812
As devices that have been cleared for marketing and being investigated in accordance with its cleared indications and cleared labeling, the Study entitled "*A Randomized, Prospective Study Comparing Fortiva vs. Strattice in Patients Undergoing Open Primary Ventral Hernia Repair"* is exempt from IDE regulations according to 21 CFR 812.2(c) (2).

A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

2.1 Treatments

The study will involve participants who are planning to undergo an elective large, complex abdominal wall hernia repair. The specific definition of this population is described in the Inclusion/Exclusion criteria. Participants must be able to participate in the informed consent process and be willing to adhere to the follow up required for this two (2) year study. The treatment includes hernia repair reinforcement with one of the following two hernia repair meshes:

- Fortiva™ Porcine Dermis
- Strattice™ Reconstructive Tissue Matrix

Fortiva™ Porcine Dermis is an implantable device comprised of non-crosslinked acellular porcine dermis that has been processed via the Tutoplast tissue sterilization process, terminally sterilized and is stored hydrated and ready to use. The implant is designed to be used in soft tissue repair and provides a strong, biocompatible scaffold that incorporates into host tissue.

Strattice™ Reconstructive Tissue Matrix is an acellular reconstructive tissue matrix designed to support tissue regeneration. It is derived from porcine dermis, which undergoes non-damaging proprietary processing that removes cells and significantly reduces the key component believed to play a major role in the xenogeneic rejection response.

2.2 Surgical Technique:

The major source of structural integrity and strength of the abdominal wall is provided by the musculofascial layer. The main paired abdominal muscles include the external oblique muscles, internal oblique muscles, transversus abdominis muscles, and rectus abdominis muscles and their respective aponeuroses, which are interdigitated with each other, and provide core strength and protection to the abdominal wall viscera. The integrity of the abdominal wall is essential not only to protect the visceral structures but also to stabilize the trunk and to aid trunk movement and posture.

Complex abdominal wall defects, including incisional abdominal wall hernias, are a challenging surgical problem. Incisional hernias occur in 10 to 23 percent of open abdominal laparotomies, with recurrence rates reported between 18 and 50 percent (deHartog, et al, 2008[14]; Lowe et al. 2000[15], Sailes et al, 2011 [16].). The Component Separation Technique (CST), a type of rectus abdominis muscle advancement flap, was first used to reconstitute the linea alba, reduce abdominal wall tension, and provide a dynamic abdominal wall in patients with large abdominal wall defects (Ramirez et al. 1990[17]). CST allows reconstruction of a large defect without requiring a free distant transposition flap (de Vries et al. 2003)[18]. The advantages of CST are that it restores structural support of the abdominal wall, provides stable vascularized soft tissue coverage, and optimizes aesthetic appearance of complex abdominal wall defects and giant midline abdominal wall hernias (Shestak et al. 2000)[19]. In this protocol, abdominal wall mobilization will be conducted in an attempt to bring the fascia together. If this is unable to be completed with circumferential undermining, component separation will be performed bilaterally.

Patients will then be randomized 1:1 to one of two treatment assignments:

- Fortiva™ Porcine Dermis retrorectus/underlay
- Strattice™ Reconstructive Tissue Matrix retrorectus/underlay

Procedure: After the abdominal wall mobilization is completed, and the Investigator determines that the primary fascial closure can be obtained, the assigned implant will be prepared according to the manufacturer's instructions and will be immediately available for the surgery.

We will utilize the Rives-Stoppa technique which begins by vertically incising the posterior rectus sheath 0.5-1cm from its medial edge. The posterior rectus sheath is separated from the rectus muscle thereby creating a retromuscular plane. This plane is developed bilaterally until the linea semilunaris preserving the perforators to the rectus muscle. After this is completed, the implant will be implanted in the retrorectus position assuring at least 3-5 cm of overlap of the defect with normal tissue. (If this technique still does not allow for primary closure, the investigator may alternatively perform a posterior component separation (Novitsky et al. or anterior component separation as per the investigators decision).

Please note that the peritoneum will be closed prior to securing the implant with a running #0 Vicryl suture. Then utilizing a parachute technique, full thickness (through fascia and implant) No. 1 PDS suture will be sewn in an interrupted fashion to implant. Please note that two (2) sutures will be placed inferiorly in Cooper's ligament as well as two (2) sutures superiorly in the subcostal area with #1 PDS as appropriately needed to secure the implant as per the investigator. A Central suture will also be placed to ensure appropriate placement between these sutures. The investigator will be sure that the implant is sewn in with moderate tension. The overlying fascia will be closed with simple interrupted No.1 PDS suture in vertical mattress or Figure of 8s fashion (as per the investigator) over the biologic implant. If the fascia is not able to be entirely closed (a bridge of implant exists without overlying fascia), the subject will be withdrawn from the study and will be considered a "screen failure". Data captured up until this point will not be included in the primary analysis. Please note that if the retrorectus space is obliterated, the implant may be placed beneath the peritoneum and again sewn in via a parachute technique with #1 PDS in a simple interrupted fashion incorporating fascia, peritoneum and implant. After the implant has been secured, the fascia is closed in vertical mattress fashion with #1 PDS over the implant.

2.3 Study Duration

Subjects will participate in this study for up to two (2) years. Participants will be followed until hospital discharge and will be seen/contacted by an Investigator and/or study team member for follow up visits at six (6) weeks, three (3) months, six (6) months and 12 months and 24 months. Once a subject has been diagnosed with a true hernia recurrence (either by physical exam or by CT Scan), he/she will be followed only for the planned re-operation (if indicated) and details of the etiology of the recurrence will be captured in the subject's study binder (CRF), when available. The subject will only be followed to capture information about the re-operation once a recurrence is diagnosed.

2.4 Study Endpoints

2.4.1 Primary Endpoints

The primary objective of this study is to compare the incidence of true hernia recurrence (true defect in the implant repair in which intra-abdominal contents are protruding through the defect) at or before 1 year between the Fortiva™ Porcine Dermis group compared with Strattice™ Reconstructive Tissue Matrix group.

2.4.2 Secondary Endpoints

- Recurrent hernias (functional hernias) requiring surgical intervention
- True recurrence at 24 months
- Evidence of Eventration/Hernia Recurrence (Radiographic)
- Fluid collection (Seroma, Hematoma)
- Surgical Site Infections
- Systemic Infections
- Enterocutaneous Fistula
- Dehiscence
- Implant failure requiring partial or total removal
- Patient satisfaction (using the SF-36 questionnaire) at Baseline, 3 months, 6 months, 12, and 24 months.
- Days to discharge
- Pain measured using the Visual Analog Scale for discomfort at Baseline, 3 months, 6 months, 12 months, and 24 months.
- Patient contentment with the cosmetic results at 12 months, 24 months and/or at the time of study withdrawal except for patients who have been withdrawn due to recurrence.

2.4.3 Safety Endpoints

- Type of Adverse Events (volunteered and elicited).
- Frequency of Adverse Events (volunteered and elicited).

III. Statistical Design

This study is a single-center prospective, randomized study evaluating Fortiva Porcine Dermis vs. Strattice Reconstructive Tissue Matrix in complex hernia repair. Up to 120 total subjects will be randomized in a 1:1 ratio.

3.1 Sample Size

Patients will be randomized at a 1:1 ratio. A total of 120 patients, 60 Strattice and 60 Fortiva patients will be enrolled. This sample size will give the study a 95% significance level and 80% power and shall provide preliminary data and benchmark evidence for direct comparison of two post-market biologic mesh materials when used as reinforcement in large abdominal hernias. The analysis also contemplates a 15 to 20% dropout rate for the primary outcome.

Power analysis and sample size determination is based on Log-rank test for equality of recurrence rates over time during the study between groups. The hazard rates of recurrence are key quantities. Often the hazard rates are very hard to obtain. However, based on the mathematical relationships of hazard function and recurrence function, we can derive the hazard rate from either of two related quantities which are

often reported in literature –(1) the proportion of recurrence-free during the study period or (2) median recurrence-free time, from Kaplan-Meier product limit survival curve.

3.2 Statistical Plan

Given the 1:1 randomized nature of the clinical trial and to preserve the inherent characteristics of the randomization, analysis by intention-to-treat (ITT) is chosen. This type of analysis compares the study groups in terms of the treatment to which they were randomly allocated, irrespective of the treatment they actually received or other trial outcomes. Regardless of protocol deviations and participant compliance or withdrawal, analysis is performed according to the assigned treatment group. This type of analysis will also help to demonstrate if there is superiority of one mesh over the other.

If there is no superiority of one mesh over the other, analysis will be performed using the same outcomes to assess if there is equivalence between both meshes. This will demonstrate that there is no clinically significant difference between the two treatment arms.
For statistical analysis, these outcomes can be classified into two measurement scales- continuous and categorical. For continuous outcome, mean and standard deviation, median and range for each group will be calculated. ANOVA will be used to compare the difference in the means among the two groups when data are reasonably normally distributed. Otherwise, non-parametric ANOVA will be used. For categorical data, proportion will be obtained for each outcome, along with 95% CI derived from exact method. Difference in the proportions among the four groups will be compared using Fisher's exact test.

3.3 Study Population

The study involves consenting adults 18 years of age and older with a large, complex abdominal wall hernia. The specific definition of this population is described in the Inclusion/Exclusion criteria.

Given the 1:1 randomized nature of the clinical trial and to preserve the inherent characteristics of the randomization, analysis by intention-to-treat (ITT) is chosen. This type of analysis compares the study groups in terms of the treatment to which they were randomly allocated, irrespective of the treatment they actually received or other trial outcomes. Regardless of protocol deviations and participant compliance or withdrawal, analysis is performed according to the assigned treatment group. This type of analysis will also help to demonstrate if there is superiority of one implant over the other.

If there is no superiority of one implant over the other, analysis will be performed using the same outcomes to assess if there is equivalence between both implants. This will demonstrate that there is no clinically significant difference between the two treatment arms.

3.4 Interim Analysis

Post Market Surveillance Interim Analysis

As this is a post-market study, the data will also support RTI Surgical requirements for post-market surveillance. At the request of regulatory agencies, interim data will be summarized approximately every 12 months. This summary will list the clinical outcomes as well as any adverse events that have been reported since the start of the study. While patient data (no personal identifiers, only subject number will

be included) will be un-blinded for this summary, this will only be for internal use at RTI and for appropriate regulatory or notified bodies. The patient and treating independent reviewer will remain blinded throughout the course of this study.

IV. Potential Risks

The planned surgical intervention for the treatment of the ventral hernia is part of the routine clinical care for the patient. Therefore, the surgical intervention itself is associated with several risks to the patient (e.g. infection, pain, etc.), however, the participation in this study is not associated with any additional risks that would not otherwise be encountered during the normal progression of treatment for this condition. The hernia repair will follow standard of care with one of two FDA cleared hernia repair implants for their intended applications.

V. Study Participants

Subjects will be identified by the investigators and/or personnel assigned by the investigators, as patients with a large complicated ventral hernia expected to be repaired with porcine derived dermal matrices. The inclusion criteria for subject selection are designed to broadly capture the subset of patients where surgeons are already currently using porcine derived dermal matrices. It is not intended to usurp clinical judgment, nor advocate that modifiable patient behaviors, like smoking, not be modified in order to include a subject. Rather the criteria are designed to be inclusive of patients with large, complex hernias, particularly those in patients without acute, but at greater risk for, surgical site infections.[17]

5.1 Informed Consent

Written informed consent will be obtained from each subject before any study procedure takes place. Informed consent will be administered by the investigator (or designee).

5.2 Eligibility Criteria

5.2.1 Inclusion Criteria

- 18 years of age or greater
- Have a BMI < or equal to 40
- Have a pre-operative estimated hernia defect of 200 cm2 OR multiple hernia defects whose combined area is ≥ an estimated 200 cm2. Patients whose defects do NOT meet or exceed 200 cm2 intra-operatively will be withdrawn from the study and will be considered an intra-operative screen failure
- Have no contraindications to the test material (s)
- Have a life expectancy greater than 1 year in the opinion of the Investigator
- Able to provide informed consent
- Able and willing to return for scheduled study visits over 2 years post-operatively (following research related surgery)

5.2.2 Exclusion Criteria

- < 18 years of age
- Subject is determined to have an American Society of Anesthesiologists'(ASA) physical class of 4, 5, or 6
- Have a BMI >40
- Have a hernia estimated to be <200 cm^2
- Have abdominal loss of domain such that the operation would be impractical or would adversely affect respiratory or cardiovascular function to an unacceptable degree in the opinion of the investigator
- Participation in an investigational drug or device study that would impact the safety or scientific integrity of this study (in the opinion of the Investigator and with the approval of the Sponsor) within the past 6 weeks prior to enrollment into this trial
- Have active necrotizing fasciitis or any other known active local or systemic infection
- Have a known collagen metabolism disorder or any medical condition that could interfere with normal tissue healing process as determined by the Investigator
- Have a known active malignancy present and/or had chemotherapy 12 weeks prior to screening or planned chemotherapy within 12 weeks of enrollment with exception of BCC or SCC
- Have known moderate to severe cirrhosis which in the opinion of the Investigator would impact the outcome of this trial
- Have a life expectancy less than 1 year
- Be unable to participate in the informed consent process
- Be unable or unwilling to return for scheduled study visits over the 2 year post-operative assessment period
- Received high dose steroids (>-100mg of prednisone) within the past 6 weeks
- Known tobacco use within the past 6 weeks or positive serum cotinine test at time of admission (patients who chew tobacco may be included at the discretion of the surgeon)
- Uncontrolled diabetes (i.e. known HbA1C value > 7% within the last 6 weeks)
- History of drug addiction (recreational drugs, prescription drugs or alcohol) that in the Investigator's opinion may interfere with protocol assessments and/or the subject's ability to complete the required follow up
- Pregnancy and/or breastfeeding

- Enterocutaneous fistula
- Ventral hernia repairs involving active infection
- Planned use of external VAC dressing intra-operatively

5.3 Enrollment and Subject Number Identifiers

5.3.1 Enrollment

Upon signing an approved Informed Consent Form subjects will be assigned a unique subject number.

5.3.2 Randomization

Patients who are consented and enrolled in the study will be randomized to receive either one of the two hernia repair implant interventions. Randomization will be 1:1. Patient numbers were allocated to a study arm based on pre-established randomization tables. Randomization tables were created using ranblock.exe (Menne Biomed Software, Tübingen, Germany). Sealed envelopes were prepared with patient specific numbers and provided to the site. If a patient is withdrawn after they have been assigned a number, the envelope with the corresponding patient number will be considered non-transferable and may not be forwarded to another patient. The subject will be blinded to their treatment arm, but the surgeon will not.

The physician should NOT disclose the treatment to the subject.

Having the investigator blinded to the treatment assignment prior to randomization reduces enrollment bias.

5.3.3 Subject Withdrawal and Discontinuation

Subjects may withdraw consent to participate at any time during the study for any reason.
The Investigator may also withdraw a subject from the study if the subject:

i. Is in deviation of the protocol
ii. Experiences a serious or intolerable AE
iii. Develops symptoms or conditions listed in the exclusion criteria during the course of the study
iv. Requests an early discontinuation for any reason

Information regarding all withdrawn or lost-to-follow-up subjects will be documented on the Study Disposition Form. Patients will either complete all the necessary study requirements or their participation in the study may prematurely end for one or more reasons. Patients will be considered "Withdrawn" due to: death, a concurrent illness that prohibits continued participation, the Investigator elects to withdraw the participant due to reasons listed above or because he/she voluntarily withdraws consent at any time during the study for any reason. Such withdrawals shall be documented on the Study Disposition Form. All available information concerning death or concurrent illness should be documented and evaluated for adverse event reporting. If the participant withdraws his/her consent, he/she should be asked (when possible and without coercion) the reason for the decision and notified that data already collected will continue to be

part of the study as per the consent form he/she signed at the time of enrollment. No further study procedures will take place after the participant requests to be withdrawn from the study.

5.3.4 Replacements

Subjects who prematurely discontinue may be replaced at the Sponsor's discretion.

5.3.5 Sponsor or Regulatory Agency Termination of the Study

Although the Sponsor (RTI Surgical, Inc.) intends to complete the study, it reserves the right to discontinue the study at any time for clinical or administrative reasons, or if required by applicable regulatory agencies.

VI. Study Visits

6.1 Baseline/Visit 1:

After signing the approved ICF, subjects who agree to participate will have Visit 1, where eligibility will be reviewed and the staff will perform the following:

1. Review all inclusion/exclusion criteria
2. Record demographic information
3. Medical, Surgical, and Social history
4. Review of systems with Physical Exam
5. Vital Signs (including height and weight)
6. Record concomitant medications (Record medications subject has been taking within 21 days prior to baseline and through the duration of the study.
7. Obtain Pre-operative lateral and frontal photographs with subject sitting and standing (when physically capable). For subjects who are not able to position themselves in a specific manner for the photograph due to physical limitations, the reason for this will be recorded in the subject's study record and this will not be considered a protocol deviation.
8. The patient will complete the following questionnaires, while the site staff will review these forms for completion:
    a. VAS
    b. SF 36

6.2 Visit 2 (Day of Surgery):

If the day of surgery is different from the baseline visit study staff will review all inclusion/exclusion criteria to ensure the participant remains eligible for enrollment. The surgery visit must be completed within 60 days of the baseline visit. If the surgery visit does not fall within 60 days of the baseline visit, the baseline procedures must be repeated.

6.2.1 Data to be collected intra-operatively:

1. Documentation of indication for surgery (i.e. incisional hernia, re-do hernia repair, etc.)
2. Documentation of size and location of hernia defect
3. Operative start and finish times
4. Determine if the subject has an active infection and if so, subject is withdrawn from study and is considered a "screen failure"

5. Determine if subject's abdomen is unable to be closed primarily and if so, subject is withdrawn from study and is considered a "screen failure"

6. Operative procedure details including all research related information (detail in OR Notes) ***Make sure all details are documented in the OR note (i.e. sutures used and where, number of drains inserted and where, overlap, etc. when possible)
7. Type and dimensions of graft used
8. Product and serial numbers of graft used
9. Fixation procedures
10. Concomitant procedures
11. Photographic documentation of graft placement prior to closure, post-closure
12. Complications during surgery (note any and all complications including uncontrolled bleeding, subject becoming unstable, error with mesh placement, etc.) and record these events as AE/SAE's as applicable
13. Medications given during surgery

6.3 Visit 3 (Hospital Discharge-2 days):

1. General physical examination and surgical site evaluation
2. Lateral and frontal photographs performed with subject sitting and standing (when physically capable). For subjects who are not able to position themselves in a specific manner for the photograph due to physical limitations, the reason for this will be recorded in the subject's study record and this will not be considered a protocol deviation
3. Adverse events evaluation (graft failure, dehiscence, enterocutaneous fistulas, seromas, wound infection, systemic infections, bleeding, etc.)
4. Return to OR for additional repair or graft removal (scheduled or date of return)
5. Review Medications (After surgery only medications that could impact healing will be recorded including but not limited to steroids, antibiotics)
6. Use of Wound V.A.C.® and reason for use
7. Date(s) of drain(s) removal, reason for drain (s) removal (i.e. drains have been in place for 7 days and/or the 24 hour fluid collection is < 30 cc /day, or any other reason removed).
8. Physical evaluation for hernia recurrence

***Once a subject has been diagnosed with a true hernia recurrence (either by physical exam or by CT Scan), he/she will be followed only for the planned re-operation (if indicated) and details of the etiology of the recurrence will be captured in the subject's study binder (CRF), when available. The subject will only be followed to capture information about the re-operation once a recurrence is diagnosed.

***There is no need to capture mesh related data or to conduct follow up visits between the diagnosis of recurrence and the operation for the recurrence. If a participant is not scheduled for a re-operation, his/her study participation will end at this point and this information will be documented on the CRF.

9. Clinical evidence of eventration, implant failure, implant related complications, etc. Photographs of the surgical site may be taken to document evidence of adverse events, eventration, implant failure, implant related complications, etc.

6.4 Visit 4 (6 weeks Post-Operative +/-One Week):

General physical examination and surgical site evaluation

1. Lateral and frontal photographs performed with subject sitting and standing (when physically capable). For subjects who are not able to position themselves in a specific manner for the photograph due to physical limitations, the reason for this will be recorded in the subject's study record and this will not be considered a protocol deviation
2. Adverse events evaluation (graft failure, dehiscence, enterocutaneous fistulas, seromas, wound infection, systemic infections, bleeding, etc.)
3. Return to OR for additional repair or graft removal (scheduled or date of return)
4. Review Medications (After surgery only medications that could impact healing will be recorded including but not limited to steroids, antibiotics)
5. Use of Wound V.A.C.® and reason for use.
6. Date(s) of drain(s) removal, reason for drain (s) removal (i.e. drains have been in place for 7 days and/or the 24 hour fluid collection is < 30 cc /day, or any other reason removed).
7. Physical evaluation for hernia recurrence

   ***Once a subject has been diagnosed with a true hernia recurrence (either by physical exam or by CT Scan), he/she will be followed only for the planned re-operation (if indicated) and details of the etiology of the recurrence will be captured in the subject's study binder (CRF), when available. The subject will only be followed to capture information about the re-operation once a recurrence is diagnosed.

***There is no need to capture implant related data or to conduct follow up visits between the diagnosis of recurrence and the operation for the recurrence. If a participant is not scheduled for a re-operation, his/her study participation will end at this point and this information will be documented on the CRF.

8. Clinical evidence of eventration, implant failure, implant related complications, etc. Photographs of the surgical site may be taken to document evidence of adverse events, eventration, implant failure, implant related complications, etc.

6.5 Visit 5 (3 months Post-Operative +/-14 days):

1. General physical examination and surgical site evaluation
2. Lateral and frontal photographs performed with subject sitting and standing (when physically capable). For subjects who are not able to position themselves in a specific manner for the photograph due to physical limitations, the reason for this will be recorded in the subject's study record and this will not be considered a protocol deviation
3. Adverse events evaluation (graft failure, dehiscence, enterocutaneous fistulas, seromas, wound infection, systemic infections, bleeding, etc.)
4. Return to OR for additional repair or graft removal (scheduled or date of return)
5. Review Medications (After surgery only medications that could impact healing will be recorded including but not limited to steroids, antibiotics)
6. Use of Wound V.A.C.® and reason for use.
7. Date(s) of drain(s) removal, reason for drain (s) removal (i.e. drains have been in place for 7 days and/or the 24 hour fluid collection is < 30 cc /day, or any other reason removed).
8. Patient Satisfaction form (SF-36)
9. Physical evaluation for hernia recurrence

   ***Once a subject has been diagnosed with a true hernia recurrence (either by physical exam or by CT Scan), he/she will be followed only for the planned re-operation (if indicated) and details of the etiology of the recurrence will be captured in the subject's study binder (CRF), when available. The subject will only be followed to capture information about the re-operation once a recurrence is diagnosed.

   ***There is no need to capture implant related data or to conduct follow up visits between the diagnosis of recurrence and the operation for the recurrence. If a participant is not scheduled for a re-operation, his/her study participation will end at this point and this information will be documented on the CRF.

10. Clinical evidence of eventration, implant failure, implant related complications, etc. Photographs of the surgical site may be taken to document evidence of adverse events, eventration, implant failure, implant related complications, etc.
11. VAS

6.6 Visit 6 (6 months Post-Operative +/-28 days):

1. General physical examination and surgical site evaluation
2. Lateral and frontal photographs performed with subject sitting and standing (when physically capable). For subjects who are not able to position themselves in a specific manner for the photograph due to physical limitations, the reason for this will be recorded in the subject's study record and this will not be considered a protocol deviation
3. Adverse events evaluation (graft failure, dehiscence, enterocutaneous fistulas, seromas, wound infection, systemic infections, bleeding, etc.)

4. Return to OR for additional repair or graft removal (scheduled or date of return)
5. Review Medications (After surgery only medications that could impact healing will be recorded including but not limited to steroids, antibiotics)
6. Use of Wound V.A.C.® and reason for use.
7. Date(s) of drain(s) removal, reason for drain (s) removal (i.e. drains have been in place for 7 days and/or the 24 hour fluid collection is < 30 cc /day, or any other reason removed).
8. Patient Satisfaction form (SF-36)
9. Physical evaluation for hernia recurrence

***Once a subject has been diagnosed with a true hernia recurrence (either by physical exam or by CT Scan), he/she will be followed only for the planned re-operation (if indicated) and details of the etiology of the recurrence will be captured in the subject's study binder (CRF), when available. The subject will only be followed to capture information about the re-operation once a recurrence is diagnosed.

***There is no need to capture implant related data or to conduct follow up visits between the diagnosis of recurrence and the operation for the recurrence. If a participant is not scheduled for a re-operation, his/her study participation will end at this point and this information will be documented on the CRF.

10. Clinical evidence of eventration, implant failure, implant related complications, etc. Photographs of the surgical site may be taken to document evidence of adverse events, eventration, implant failure, implant related complications, etc.
11. VAS

6.7 Visit 7 (12 months Post-Operative +/-28 days):

1. General physical examination and surgical site evaluation
2. Lateral and frontal photographs performed with subject sitting and standing (when physically capable). For subjects who are not able to position themselves in a specific manner for the photograph due to physical limitations, the reason for this will be recorded in the subject's study record and this will not be considered a protocol deviation
3. Adverse events evaluation (graft failure, dehiscence, enterocutaneous fistulas, seromas, wound infection, systemic infections, bleeding, etc.)
4. Return to OR for additional repair or graft removal (scheduled or date of return)
5. Review Medications (After surgery only medications that could impact healing will be recorded including but not limited to steroids, antibiotics)
6. Use of Wound V.A.C.® and reason for use.
7. Date(s) of drain(s) removal, reason for drain (s) removal (i.e. drains have been in place for 7 days and/or the 24 hour fluid collection is < 30 cc /day, or any other reason removed).
8. Patient Satisfaction form (SF-36)
9. Physical evaluation for hernia recurrence

***Once a subject has been diagnosed with a true hernia recurrence (either by physical exam or by CT Scan), he/she will be followed only for the planned re-operation (if indicated) and details of the etiology of the recurrence will be captured in the subject's study binder (CRF), when available. The subject will only be followed to capture information about the re-operation once a recurrence is diagnosed.

***There is no need to capture implant related data or to conduct follow up visits between the diagnosis of recurrence and the operation for the recurrence. If a participant is not scheduled for a re-operation, his/her study participation will end at this point and this information will be documented on the CRF.

10. Clinical evidence of eventration, implant failure, implant related complications, etc. Photographs of the surgical site may be taken to document evidence of adverse events, eventration, implant failure, implant related complications, etc.
11. VAS
12. Patient contentment with the cosmetic results

6.8 Visit 8 Phone Call Follow Up (24 months Post-Operative +/-28 days):

1. Recurrence Information (ask participant if they have been evaluated and or treated for recurrence)
2. Adverse events evaluation (graft failure, dehiscence, enterocutaneous fistulas, seromas, wound infection, systemic infections, bleeding, etc.)
3. Return to OR for additional repair or graft removal (scheduled or date of return)
4. Review Medications (After surgery only medications that could impact healing will be recorded including but not limited to steroids, antibiotics)
5. Use of Wound V.A.C.® and reason for use.
6. Patient Satisfaction form (SF-36)*
7. VAS*
8. Patient contentment with the cosmetic results*

*The subjective questionnaires entitled Visual Analog Scale (VAS), SF-36, and Patient Contentment cannot be completed visually by the subject. Therefore, for the VAS, patients will be asked to rate their pain on a scale of 1-10. Patients will be asked questions on the SF-36 and Patient Contentment and the answers will be transcribed by designated study staff.

6.9 Unplanned Visit

The procedures performed at an unplanned visit will depend on the nature of the visit. The procedures suggested include:

1. Physical assessment to include BMI, general health, etc. (if indicated)
2. Physical examination of surgical site (if indicated)
3. Lateral and frontal photographs performed with subject sitting and standing (when physically capable). For subjects who are not able to position themselves in a specific manner for the

4. photograph due to physical limitations, the reason for this will be recorded in the subject's study record and this will not be considered a protocol deviation.
5. Radiographic evidence of recurrence only if clinically indicated
6. Newly diagnosed medical issues
7. Medication updates, if any
8. Adverse events since last visit (i.e. graft failure, enterocutaneous fistula, seromas, wound infection, systemic infection, bleeding, etc.)
9. Physical evaluation for hernia recurrence

   ***Once a subject has been diagnosed with a true hernia recurrence (either by physical exam or by CT Scan), he/she will be followed only for the planned re-operation (if indicated) and details of the etiology of the recurrence will be captured in the subject's study binder (CRF), when available. The subject's will only be followed to capture information about the re-operation once a recurrence is diagnosed.

   ***There is no need to capture implant related data or to conduct follow up visits between the diagnosis of recurrence and the operation for the recurrence. If a participant is not scheduled for a re-operation, his/her study participation will end at this point and this information will be documented on the CRF.
10. Clinical evidence of eventration, implant failure, implant related complications, etc. Photographs of the surgical site may be taken to document evidence of adverse events, eventration, implant failure, implant related complications, etc.
11. Return for repair since last visit.
12. Patient Satisfaction form (SF-36)*
13. VAS*
14. Patient contentment with cosmetic results*

*IF the subjective questionnaires entitled Visual Analog Scale (VAS), SF-36, and Patient Contentment cannot be completed visually by the subject for the VAS, patients will be asked to rate their pain on a scale of 1-10. Patients will be asked questions on the SF-36 and Patient Contentment and the answers will be transcribed by designated study staff.

6.10 Schedule of Events:

Schedule of Events

	Visit 1 Baseline	Visit 2 Surgery	Visit 3 Hospital Discharge (-2 days)	Visit 4 6 Weeks (+/- 1 week)	Visit 5 3 Months (+/- 14 days)	Visit 6 6 Months (+/- 28 days)	Visit 7 12 Months (+/- 28 days)	Visit 8 Telephone 24 Months (+/- 28 days)
Informed Consent	X							
Physical Exam	X		X	X	X	X	X	
Medical, Social, Surgical History	X	X						
Medications	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
SF36*	X				X	X	X	X
VAS*	X				X	X	X	X
Clinical Evaluation	X		X	X	X	X	X	
Photographs	X	X	X	X	X	X	X	
Patient Contentment with cosmetic results*							X	X

*If withdrawn early complete patient contentment cosmetic results.
*If the subjective questionnaires entitled Visual Analog Scale (VAS), SF-36, and Patient Contentment cannot be completed visually by the subject, for the VAS, patients will be asked to rate their pain on a scale of 1-10. Patients will be asked questions on the SF-36 and Patient Contentment and the answers will be transcribed by designated study staff.

VII. Safety Assessments

7.1 Safety Evaluations

For the purpose of this post-marketing trial, only adverse events or serious adverse events that are related to the surgical procedure or device will be recorded. Safety will be assessed by recording the nature, intensity and duration of all device related adverse events (AEs) and their relationship to the device.

7.2 Adverse Event Reporting

An Adverse Event (AE) is defined as any untoward medical occurrence in a subject enrolled into this study, regardless of its causal relationship to treatment. The Investigator is responsible for recording all AEs related to the surgical procedure or the device that are observed or reported by the subject during the study for the Sponsor. The collection of AE's shall begin immediately after the patient has had a porcine derived dermal matrix surgically implanted. AEs related to the surgical procedure or the device that occur from surgery through completion of the final follow-up visit, whether observed by the investigator or by the subject, shall be reported in detail on the appropriate CRFs and followed to resolution or the end of the subject's study participation.

In the event a subject reports an AE outside the scheduled clinical visit, it will be assessed at the earliest opportunity by the Investigator.
In following up AEs, attempts will be made to obtain as much information as possible about event evolution and outcome. Every effort will be made to follow the subject until resolution of the AE.

Adverse Event/Serious Adverse Evaluation

Degree of Impairment

The Investigator will evaluate the relationship of the adverse event to the degree of impairment using the following:

1. Mild: The AE is transient and easily tolerated by the subject; no limitation of usual activities
2. Moderate: The AE causes the subject discomfort and interrupts the subject's normal activity; some limitation of usual activities
3. Severe: The AE is life threatening, results in permanent impairment of a body function, causes permanent damage to a body structure, or necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure; inability to carry out usual activities

Relationship of AE/ SAE to Implant

The Investigator will evaluate the relationship of the AE/SAE to the use of the implanted mesh according to the following:

1. Definite: The AE/SAE follows a reasonable temporal sequence from the implantation of the implant and/or is directly attributable to the use of the implant within the repair site.

2. Possible: The AE/SAE follows a reasonable temporal sequence following the implantation of the implant and the possibility of the implant's involvement cannot be excluded. However, other factors related to the surgical procedure, underlying disease, concomitant treatment or medications are presumable.

3. Unlikely: The AE/SAE has an improbable temporal sequence from the implantation of the implant or it can be reasonably explained by other factors, including surgical procedure, underlying disease, concomitant treatment or medications.

4. Not Related: The AE/SAE has no temporal sequence from the implantation of the implant or it can be explained by other factors, including surgical procedure, underlying disease, concomitant treatment or medications.

For the purposes of this study, significant adverse events will be documented and reported to the study PI, Sponsor, and appropriate oversight committee at the institution per institutional protocol

7.3 Serious Adverse Events

An Adverse Event is serious if:

- It results in death
- It is life threatening (the subject is at immediate risk of dying from the adverse experience)
- It requires inpatient hospitalization or prolongs existing hospitalization
- It results in persistent or significant disability/incapacity
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse device effect when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

SAEs will be recorded in the CRF if they occurred as follows:

After a subject received treatment and throughout the subject's follow-up period. After the subject's follow-up period, and for which a causal relationship to treatment with either randomization group cannot be ruled out. Follow-up period is defined as the protocol-stipulated period or, for subjects prematurely withdrawn from a study, the duration of subject's participation.

Study staff are instructed to report all SAEs to the PI and Sponsor within 24 hours of becoming aware of the SAE. All follow-up SAE reports are to be completed and provided within 7 calendar days to the Sponsor, allowing time for more complete reports.

All Serious Adverse Events (SAEs) must be reported to:

Clinical Projects
RTI Surgical, Inc.
11621 Research Circle
Alachua, FL 32615-2650
(P) 386-418-8888
(F) 386-418-1627 **and**
RTI Customer Service
800-624-7238
Fax: 386-462-1837

In addition to documenting SAEs on the Case Report Forms, a separate SAE form must also be completed. SAEs must also be reported either by telephone, email or by FAX by the Investigator, study coordinator, or other designated study personnel, or clinical research associate within twenty-four (24) hours of becoming aware of the SAE. Follow up information must be reported as it becomes available, this may include records such as subject X-Rays, Admission and Discharge summaries, etc.

7.4 Unanticipated Adverse Events/Unanticipated Serious Adverse Events

An unanticipated adverse event/serious adverse event is any unexpected untoward event or medical occurrence in a study subject that is not consistent with the known, predicted possible effects of the research protocol. An unanticipated adverse event/serious adverse event can therefore be any unanticipated, unfavorable, and unintended sign including an abnormal laboratory finding, symptom, or disease temporally associated with the study that was not listed in the protocol or consent form. This includes any experience that suggests a significant hazard, contraindication, side effect, or precaution.

Unanticipated Adverse Events (UAEs) shall be reported to the Sponsor within two to five (2-5) days of event notification and Unanticipated Serious Adverse Events (SUAs) within 24 hours of event notification (report unanticipated serious adverse events as soon as possible); to the IRB and to any medical oversight committees within seven (7) days of event notification unless institution guidelines require earlier reporting. Investigators should be vigilant in collecting as much information surrounding the event as possible, such that the investigator's best evaluation regarding the degree of impairment and the relationship between the surgical procedure and the adverse event can be made.

VIII. Human Subject Protection Requirements

The Principal Investigator (PI) is required to provide an Institutional Review Board (IRB) with all appropriate materials for review and approval prior to commencing any study related procedures. The study may not be initiated unless/until the IRB Committee provides written approval of the proposed clinical study and an approved and IRB stamped Informed Consent Document. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB as required.

The Investigator is responsible for ensuring the study is conducted in accordance with the scheduled procedures and evaluations described in this protocol. Deviations from the protocol shall not be made without discussion with the Sponsor and IRB unless there is a safety concern where the intent of the deviation is to reduce immediate risk to the patient. In such cases, the Sponsor, the IRB, other regulatory bodies, should be notified in accordance with local requirements. Changes to the protocol may be made only when a written protocol amendment provided by the Sponsor has been signed by the Investigator and approved by the IRB and other applicable regulatory agencies in accordance with local requirements

Renewal of Human Protection training must be submitted to the Sponsor every three (3) years during the course of the study.

IX. Regulatory Requirements

Fortiva and Strattice are FDA 510(k) cleared for marketing in the United States for hernia repair. No additional regulatory approvals are required to perform this study.

X. Investigator's Responsibilities

The investigators are responsible for performing the study in full accordance with the protocol. Information regarding any centers participating in this study that do not comply with these standards will be documented.

10.1 Guidelines of Obtaining Subject Informed Consent

Written and oral information about the study in a language understandable by the subject will be given to all subjects by the investigator and/or designee. Written informed consent will be obtained from each subject before any procedures or assessments that would not otherwise be required for the care of the subject are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person (e.g., a family member) to be present during the explanation of the study.

A copy of the informed consent document to be used will be submitted by the Investigator to the IRB for review and approval prior to the start of the study. The original signed consent is retained in the subject's study records, and a copy is provided to the subject.

The ICF will comply with all applicable regulations governing protection of the participants in the study, and include the basic elements specified in 21 CFR 50.25(a).

10.2 Subject Confidentiality

The investigators must assure that the privacy of the subjects, including their personal identity and all other personal medical information, will be maintained at all times. In CRFs and other documents or material, subjects will not be identified by their names, but by an identification code (e.g., study allocated number). Personal medical information may be scrutinized for the purpose of verifying data recorded in

the CRF. This may be done by properly authorized persons on behalf of the PI or regulatory authorities. Personal medical information will always be treated as confidential.

The investigator will maintain the confidential master subject identification list that link to the subject's medical records. The subjects will be identified in the CRF with subject numbers. The Investigator should inform the subject that the records relevant to the study may be inspected by the study PI, the FDA, or other persons as required by law.

10.3 Institutional Review Board Approval

The investigator is responsible for obtaining IRB approval, if required, to conduct this study. The sponsor will assist the investigator as needed. Written confirmation of approval from the participating IRB must be provided to the sponsor prior to commencement of the study. The Investigator is also responsible for filing adverse events, annual reports and a final report to the IRB. The sponsor will assist the investigator as needed.

XI. Data Handling and Quality Assurance

11.1 Case Report Forms (CRFs) and Data Clarification Forms (DCFs):

As part of the responsibilities assumed by participating in the study, the Principal Investigator or sub-investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The Principal Investigator or sub-investigator agrees to maintain accurate CRFs/DCFs and source documentation as part of the subject case histories. The completed CRFs/DCFs are legal documents as they may be intended for submission to a regulatory agency as part of a regulatory submission. The data will be recorded on the CRFs/DCFs or other media as provided by the Sponsor.

a. These source documents may include chart notes, laboratory reports and ECG strips, X-Rays,CT scans and MRI. The reported data must be accurate, complete and verifiable from source documents.
b. All CRFs should be completed legibly in black ink. CRFs may not be completed in pencil.
c. All CRF information is to be filled in. If an item is not applicable or not done, this fact should be indicated by entering "NA" or "ND", respectively. Blank spaces should not be present unless otherwise directed. A correction should be made by striking through the incorrect entry with a single line and the corrected information should be entered adjacent to the deleted item. The correction must be initialed and dated by the person making the correction.
d. The Investigator is to record all data relating to study procedures, treatment regimen administration, safety and efficacy data using the CRFs provided by the Sponsor.
e. All corrections on source documents as well as CRFs must be made so that the original data is not obscured in any way (i.e. use of correction fluid of any kind, correction tape, erasure or any form of obliteration of data is not permitted under any circumstances).
f. Subject questionnaires may be recorded directly onto a CRF by the subject instead of transcribing from source documentation. At study initiation, the Sponsor will communicate to the Investigator any CRFs that may serve as source documentation for the study.
g. To ensure confidentiality, subjects will be identified in the CRFs only by their initials (first, middle, last) and a unique study subject number.
h. The Investigator's signature is required to attest to the accuracy of the data. All electronic records and electronic signatures, if used, must comply with applicable laws and regulations (e.g. FDA 21 CFR11).

i. Each completed CRF notebook must be reviewed, signed, and dated by the Principal Investigator in a timely manner. The completed CRF will be reviewed against source documentation at the site and will be collected by the Study Monitor as soon as is practical after completion. One copy will remain at the site in the Principal Investigator or sub-investigator's files.
j. Data Clarification Forms (DCFs) are used to request additional information and/or clarification of data already entered on a specific case report form and with its completion with dated signature(s) serves as confirmation, clarification and/or correction of the original data entry.

11.2 Monitoring of the Study:

The Study Monitor, as a representative of the Sponsor, has an obligation to follow the study closely. In doing so, the Study Monitor will visit the Principal Investigator or sub-investigator and study facility at periodic intervals, in addition to maintaining necessary telephone and letter contact. The Study Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Principal Investigator or sub-investigator and staff.

a. All aspects of the study will be carefully monitored by the Sponsor or its representative for compliance with applicable government regulation with respect to the ICH-GCP consolidated guideline and current standard operating procedures.
b. Contact Information
   Clinical Projects
   RTI Surgical, Inc.
   11621 Research Circle
   Alachua, FL 32615-2650
   386-418-8888 ext. 4344

11.3 Inspection of Records:

Principal Investigators or sub-investigators and institutions involved in the study will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to all study records. The Principal Investigator or sub-investigator should promptly notify the Sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

11.4 Regulatory Compliance:

This study must be conducted in compliance with the Declaration of Helsinki and ICH-GCP. In addition, all local, state, federal and institutional requirements will be adhered to, especially if they provide additional protection to the study subjects.

11.5 Advertising:

All potential advertising materials used to recruit subjects for this study will be submitted for approval to the Sponsor and to the relevant IRB.

11.6 Protocol Amendments:

Protocol amendments must be approved by the IRB/IEC prior to their implementation unless such changes are necessary to address immediate safety concerns for the subject.

11.7 Adherence to Protocol:

The final protocol sets forth how the study will be conducted.

a. The Investigator is required to adhere to this protocol.
b. Any reasonable alternatives, variations, or deviations from the protocol must first be approved by the Sponsor and the IRB (if applicable) unless it is required for the successful management of safety issues relating to the subject.
c. Any clarification to the protocol will be documented in the study site's Regulatory Binder.

A protocol deviation occurs when the Investigator or subject has failed to adhere to protocol requirements.

a. All deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment should be described.
b. Protocol deviations should be appropriately documented. Specific categories to be documented include but are not limited to:
    i. Subjects who enter the study even though they do not satisfy the entry criteria
    ii. Subjects who complete study visit outside of specified window.
    iii. Subjects who do not complete required study procedures.
c. Other protocol deviations to be considered include non-adherence to the protocol that results in a significant additional risk to the subject, or when there is non-adherence to FDA (or other international regulatory agency) regulations and/or ICH/GCP guidelines.
d. The Principal Investigator, sub-investigator, or designee must document and explain any protocol deviation in the subject's source documentation.
e. The IRB should be notified of all protocol deviations in a timely manner or according to their requirements.
f. Protocol deviations will also be documented by the Study Monitor during monitoring visits and reported to the Medical Monitor that may result in significant additional risk to subjects or adverse reactions and those observations will be reviewed with the Investigator.
g. The Principal Investigator or sub-investigator may implement a change from the protocol without prior Sponsor and IRB approval only to eliminate an immediate hazard to a subject.
h. If the Investigator believes that any exception to the protocol is justified for an individual subject or if the Investigator has a question concerning a subject who may not meet an entry criterion, they should contact the Clinical Projects Department at the Sponsor (RTI Surgical). If the Sponsor is in agreement that an exception is justified, then a planned protocol deviation will be written and submitted to the applicable IRB for approval prior to implementation of the change per the IRB's procedures. The original document will remain with the subject's source file at the investigator's site and the study Sponsor will be provided with copies to be maintained in the Clinical Trials Master File (CTMF).

11.8 Records Retention:

At the conclusion of the study, all Essential Documents as listed in the ICH/GCP guidelines (including relevant medical/dental records and source documents, copies of CRFs, and ICFs) for all subjects for whom the Investigator has a signed Informed Consent Statement are retained by the Investigator.

a. The retention period will be the greater of fifteen (15) years or the retention period dictated either by an agreement with the Sponsor, state or local regulations, or ICH/GCP guidelines.
b. The Investigator must inform the Sponsor in writing for approval prior to the disposal of any study-related records even if the retention requirements as stated above have been met.
c. If the Principal Investigator leaves the institution at which the study was conducted, he/she or the current representative must contact the Sponsor to make arrangements to ensure that all applicable study records as well as the study master log are retained, as outlined above, to provide for continuing access by the Sponsor and any regulatory agencies, as needed.

XII. Study Reporting Requirements

12.1 Serious Adverse Events:

By participating in this study, the Principal Investigator or sub-investigator agrees to submit reports of SAEs and Adverse Reactions according to the timeline and method outlined in the protocol, IRB/IEC policy and applicable regulations.

12.2 Continuing Annual Reviews:

The Principal Investigator or sub-investigator agrees to submit annual reports to his/her IRB/IEC as appropriate.

12.3 Financial Disclosure:

Principal Investigators and/or sub-investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under Title 21 CFR 54 and 42 USC 1320a-7h, and any other applicable federal and state law or regulation. If any relevant changes occur throughout the investigation and one (1) year following the completion of the study, the Principal Investigator and/or sub-investigator must promptly provide the updated information to the Sponsor.

12.4 Sponsor Liability:

The Sponsor is not financially responsible for further testing/treatment of any medical condition that may be detected during the screening process.

12.5 Investigator Documentation:

Prior to beginning the study, the Principal Investigator will be asked to comply with ICH/GCP guidelines and any applicable regulations by providing the following essential documents, including but not limited to:

a. An original Investigator Signature Page of the protocol.
b. An IRB/IEC-approved Informed Consent Form, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardians.
c. IRB/IEC approval of the Investigator, protocol, and Investigator's Brochure (if applicable).

d. Form FDA 1572, fully-executed, and all updates if applicable (or other international regulatory agency form, as applicable).

e. Curricula Vitae and Human Subject Protection training for the Principal Investigator, each sub-investigator, study coordinator, and any study staff participating in study related procedures and/or the informed consent process. Current licensure must be noted on the curricula vitae or a copy of the license provided. The curricula vitae must be signed and dated by the Principal Investigators and sub-investigators within one year of study start-up, indicating that they are accurate and current.

   Unless otherwise established, updated, signed and dated curricula vitae for the Principal Investigator, each sub-investigator, and applicable study staff must be submitted every two (2) years and renewal of Human Protection training must be submitted every three (3) years during the course of the study.

f. Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under Title 21 CFR 54. In addition, the Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation, at the completion of the trial and one year following the completion of the study.

g. Laboratory certifications and normal ranges for any local laboratories used by the site in accordance with Title 42 CFR 493.

XIII. Publications

Following completion of the study at all sites, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. Draft manuscripts of any public disclosure shall be provided to the Sponsor at least sixty (60) days prior to presentation or publication, in order to enable Sponsor to review and comment and take any steps necessary to protect its intellectual property rights, consistent with the Clinical Trial Agreement. If RTI identifies in the presentation or publication information that would have an adverse effect on an existing or potential patent application of RTI, the Principal Investigator will refrain from submitting such presentation or publication for up to ninety (90) days from the date it receives notice from RTI in order to afford RTI an opportunity to mitigate such adverse effect.

XIV. Investigator's Final Report

Following the completion of the study the Investigator shall participate in the preparation of an integrated clinical and statistical final study report. The final report will include a general description of the conduct of the study including pertinent protocol deviations, subject withdrawals, and a discussion of AEs, safety data, and statistical analysis. This report will be approved and signed by the Investigator.

XV. Potential Financial Risks

There are no additional financial risks to the subjects in connection with participation in this study. Participants will be compensated for their travel for follow up visits up to $100 per scheduled face to face visit.

XVI. Conflict of Interest

The Sponsor is not aware of any conflict of interest issues with the Investigators that would affect their participation in this study. The Investigator will immediately notify the Sponsor if s/he becomes aware of any such conflict of interest.

XVII. Publication of Results

At the completion of the evaluation the Investigator may publish the results in a peer- reviewed journal subject to the conditions set forth in Section 13 above and the terms of the clinical research agreement between the Sponsor and the institution at which the study is conducted. In addition, at the request of the Sponsor, the Investigator will present the results at a significant AWR related meeting/symposium.

17.1 Meetings

Applicable meetings include, but are not limited to Americas Hernia Society/World Hernia Congress, Abdominal Wall Reconstruction Conference, and American College of Surgeons.

17.2 Journals

Relevant peer-reviewed journals include, but are not limited to Hernia, Surgery, and Annals of Surgery.

Draft manuscripts of any public disclosure shall be provided to the Sponsor at least sixty (60) days prior to presentation or publication, in order to enable Sponsor to review and comment and take any steps necessary to protect its intellectual property rights, consistent with Section 13 above and the terms of the clinical research agreement.

XVIII. Study Registration

This study will be registered by the Sponsor on clinicaltrials.gov.

XX. References

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3. Dallemagne B, Kohnen L, Perretta S, Weerts J, Markiewicz S, Jehaes C (2011) Laparoscopic repair of paraesophageal hernia. Long-term follow-up reveals good clinical outcome despite high radiological recurrence rate. Ann Surg 253 (2):291-296.
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XX. INVESTIGATOR SIGNATURE PAGE

I have read and understood the protocol and agree to implement the study in accordance with the procedures set forth in the protocol and in accordance with the Sponsor's guidelines and all applicable government regulations and the International Conference on Harmonization Good Clinical Practice E6 (ICH/GCP).

I will provide adequate protocol training to my associates, colleagues and employees assisting in the conduct of this study.

I will obtain IRB or IEC approval of the Protocol and Subject ICF prior to enrollment of subjects in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the IRB/EC except when such modification is made to remove an immediate hazard to the subject.

I will ensure that a fully executed Informed Consent Form is obtained from each subject prior to the initiation of study related procedures.

I will report, within 24 hours of my knowledge, any SAE that occurs during the course of the study in accordance with the procedures described in the protocol.

I will allow the Sponsor, RTI Surgical, Inc., and its agents, as well as the US Food and Drug Administration (FDA) and other regulatory agencies, to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, ensuring subject confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify the Sponsor (RTI Surgical, Inc.) and the IRB/EC as soon as possible thereafter (no later than one week).

_____ _____

Principal Investigator Signature Date

_____

Printed Principal Investigator Name