Investigational plan

Protocol Title: Safety and efficacy of a contained electromechanical power morcellation systems for laparoscopic hysterectomy and myomectomy.

NCT#: NCT02777203

Date: 4/11/2017

Protocol Number: Pending. The study sponsor will be the Advanced Gynecologic Surgery Institute. The investigational site will be ALGH. The study will be reviewed by the Advocate Health Care Institutional Review Board (IRB) per appropriate protocol.

Objectives
The purpose of this feasibility study is to determine the safety and efficacy of using an insufflated bag for electromechanical power morcellation during laparoscopic hysterectomy and myomectomy for tissue removal. Our goal is to prove that the integrity of the bags is maintained throughout and after insufflation and power morcellation.

The hypothesis is that the bag will remain integral and there is will be no leakage from the bag during and after power morcellation using the described contained system, confirming the safety and efficacy of thesystems.

Inclusion and Exclusion Criteria
Inclusion criteria will be adult premenopausal women (equal or greater than 18 years old) at ALGH without symptoms of menopause undergoing robotic or laparoscopic total or supracervical hysterectomies or myomectomies for the indication of symptomatic uterine fibroids who are not candidates for specimen removal via mini-laparotomy incision (as deemed by the study surgeon) or who have refused mini-laparotomy and therefore require power morcellation for tissue removal.

Exclusion criteria include known or suspected malignancy, peri- or post-menopausal women diagnosed with uterine fibroids, specimen that can be removed without power morcellation (e.g., vaginally or through laparoscopic trocars), and adults unable to consent.
These patients will be screened and consented pre-operatively. The final decision on a patient's inclusion or exclusion from the study will occur intra-operatively after evaluation of the size and characteristics of the uterus.

Study-Wide Number of Subjects
As this will be a feasibility study, a maximum of 110 patients will be enrolled into the study. Over a one year time, the investigation group performs a total of 130 hysterectomies and myomectomies; therefore, we anticipate 110 patients will be enrolled in this study during a three year timeframe.

Study-Wide Recruitment Methods
Potential subjects will be patients of The Advanced Gynecologic Surgery Institute. They will be recruited pre-operatively in the office if they are scheduled to have a laparoscopic or robotic- assisted hysterectomy or myomectomy for symptomatic uterine fibroids at ALGH. The purpose, details, and consent for the study will be performed at that time. The study will then be re- discussed with the patients during the surgical consent process.

Patients currently sign a consent form for morcellation per Advocate Health Care guidelines

(Attachment A). They also sign a separate consent for morcellation in a bag specifically developed by The Advanced Gynecologic Surgery Institute (Attachment B). The alternative provided in this consent is to convert to laparotomy. The subjects will sign the existing consents as well as the research consent to participate in the study.

Study Timelines

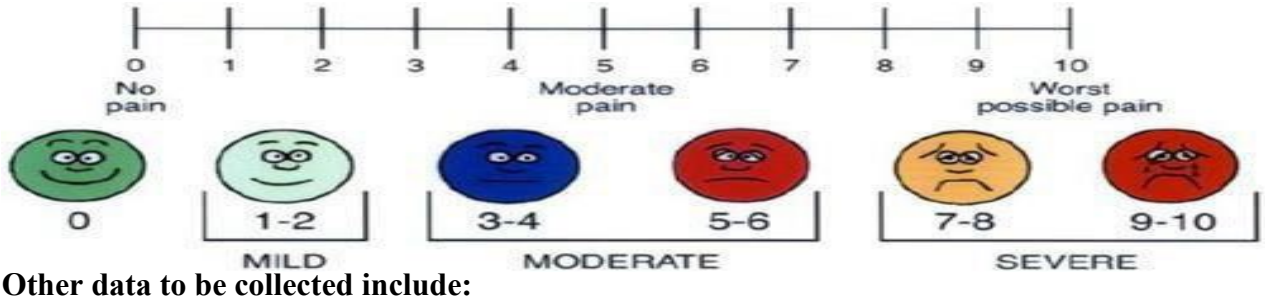
- The duration of an individual subject's participation in the study is only the time of their planned surgical hospitalization and their participation in the follow up pain assessments.
- The duration anticipated to enroll all study subjects is approximately one year.
- The estimated date for the investigators to complete this study is Fall 2016 / Spring 2017.

Study Endpoints

Primary endpoint: Leakage of egg albumin from the EcoSac bags after isolated bag morcellation or apparent leakage of specimen from the EcoSac bags during isolated bag morcellation.
Secondary endpoints:

- Intra-operative Complications (yes or no)
  - If yes to complications, please specify
- Post-operative Complications (yes or no)
  - If yes to complications, please specify
- Length of stay (hours)
- Admission (yes or no)
- Re-admission (yes or no)
  - If YES, yes to re-admission, specify reason_____
- Morcellation time (minutes) – from insertion of bag to removal of bag
- Technical issues with the use of the bag (yes or no)
- Conversion to open procedure (yes or no)
- Smooth muscle cell clusters in cytologic washings (yes or no)
- Post operative pain (Visual Analog Scale pain scale) (Figure 1)
  - Assessment times: immediate post-operative period (in the recovery room); 1 week post operatively; 2 weeks post operatively, and 4-6 weeks post operatively

Figure 1: Visual Analog Scale - Pain Scale



Other data to be collected include:

- Age
- Race
- Socioeconomic status (including educational level and annual household income)
- Weight
- Height
- Body Mass Index (BMI) (calculated)
- Specimen weight (grams)

Procedures Involved

The study will be a single center, prospective, observationalof the EcoSac 400 ECO t. Originally patients were going to be assigned to one of two arms to receive EcoSac 230 (Group 1) or EcoSac 400 ECO-T (Group 2). No random assignment method was to be utilized. Instead, the decision would have been at the surgeon's discretion. Due to improved visualization with the EcoSac 400 ECO T, and the fact that a smaller incision is needed, no patients were enrolled to the EcoSac 230 arm. Due to the fact that the EcoSac 400 ECO T was felt to be a safer procedure, the protocol now only included the EcoSac 400 ECO T.

Patients will be recruited during their pre-operative consent process. All patients will undergo a pre-operative history and physical exam, have an up to date documented pap smear within the last year, and undergo a saline-infused sonohysterogram and endometrial biopsy. Any patient with a fibroid that appears suspicious on ultrasound evaluation will be sent for magnetic resonance imaging (MRI) of their pelvis to further evaluate the fibroid.

All patients undergoing potential morcellation of a fibroid uterus currently sign a consent pre-operatively allowing this process. They will also be consented for morcellation specifically in a specimen bag.
The final evaluation and potential exclusion from the study with occur in the operating room. It will be based on the factors listed above. The alternative to morcellation is converting to laparotomy.

EcoSac 400 ECO-T (EMP 400 ECO-T)

Those patients consented and considered candidates for morcellation with the EcoSac 400 ECO-T will undergo their laparoscopic hysterectomy or myomectomy in the standard technique. A 12 mm umbilical trocar will be used as well as two to three lateral 5 mm trocars under standard technique. After removal of the uterus and/or fibroids, reconstruction of the uterus, and any additional necessary procedure and control of any bleeding, the morcellation portion of the procedure will take place.

The Espiner EcoSac 400 ECO-T will be inserted through the umbilical trocar with a blunt grasper under direct visualization, with the laparoscope placed through a lateral trocar. Once inside the abdomen, the specimen will be placed inside the bag. The accessory sleeve will be grasped through the right lateral 5 mm trocar and is pulled up through the abdominal wall until the entire sleeve isout and the opening to the sleeve is flush with the inside of the abdominal wall. The same 5 mm (non-bladed) trocar is then replaced back into the abdomen through the sleeve so that it is entering into the bag. The string to close the bag will be pulled and the bag will be brought up through the umbilical incision after the trocar is removed while simultaneously providing tension on the right lateral arm to prevent slippage. The insufflation will be hooked up to the right lateral trocar and CO_2 gas will be insufflated into the bag to a pressure of 25 mmHg. Simultaneously, existing gas will be removed from the abdomen. This higher insufflation is necessary to obtain the maximum distension of the bag. Because the insufflation is going directly into the bag and not into the abdominal cavity, the effect of the higher pressure does not cause any increased harm to the intra-abdominal organs. The laparoscope will be placed through the right lateral trocar. Under direct visualization inside the bag, the umbilical incision (where the 12 mm trocar was previously removed) will be dilated to 15 mm. The Storz Rotocut G1 Morcellator will be inserted directly through the umbilical incision and morcellation will proceed as normal. When the EcoSac 400 ECO- T is completely insufflated, it will distend to the sides of the abdominal cavity. The Storz Rotocut G1 Morcellator does not reach the end of this distended bag. Furthermore, the morcellator is placed under direct visualization, assuring no damage to the bag. Once morcellation is complete, all small pieces of tissue will be grasped with a spoon and removed. The inside of the bag will then

be irrigated allowing for removal of any small pieces from the sidewalls of the bag.

After careful inspection to ensure all small pieces are removed, one hundred milliliters of normal saline will be used to gather washings of the inside of the bag. We will perform a "washing" of the inside of the bag that pathology will evaluate for any retained fibroid pieces or cells. After performing the morcellation and removing the bag, we will place an albumin solution with blue dye inside of the bag to assess for any areas of leakage.

This specimen will be sent for cytologic evaluation to evaluate for any smooth muscle cell clusters that may represents pieces of fibroid tissue remaining in the bag prior to removal of the bag. We anticipate cytology to see inflammatory cells, reactive mesothelial cells, and rare red blood cells; but anticipate no smooth muscle cell clusters as we anticipate we will be able to remove all of the fibroid particles and pieces. The patient information will be sent via hospital secured email to the pathology department in order to waive the cytology fee. Although all small pieces will be removed with removal of the intact bag, this will give assurance to the surgeon that all of the pieces can be seen within the bag and therefore can been completely removed.

The CO_2 gas will then be removed from the bag. The right lateral trocar will be removed and the accessory sleeve will be tightly tied off at the most distal end of the sleeve. The entire bag will then be removed from the umbilical incision, pulling the accessory sleeve back through the right lateral incision and out the umbilical incision in the process. The right lateral and umbilical trocars will then be replaced and insufflation will be attached per standard protocol allowing insufflation of abdomen again to a pressure of 15mmHg. Any further portions of the procedure will be completed as needed.

The integrity of the bag will be inspected. Once the bag is removed from the abdomen, it will be taken out of the operating room to the frozen section room. Five hundred milliliters of egg albumin (from egg whites) combined with 0.5 milliliters of methylene blue will be placed into the bag to assess for any leakage. The bag will be insufflated to a pressure of 25mmHg in a box trainer. A positive result with be documented if the egg albumin solution is present on the outside of the bag or dripping from any location. In current testing with Espiner Medical Ltd., egg albumin has been shown to not leak through the EcoSac 400 ECO-T (EMP 400 ECO-T) (Attachment C). The size of egg albumin is approximately 5.5 nm with a gram molecular weight (GMW) of 45,000. Although a hydrogen atom (0.1 nm, GMW 1), water (0.2 nm, GMW 18), and DNA (2 nm) are smaller than egg albumin, viruses and cancer cells are much larger (24-200 nm and 10,000-30,000 nm, respectively) (Attachment D).
Therefore, if egg albumin is unable to leak from the bag despite insufflation, fibroid cells or potentially cancerous cells will also be unable to leak from the bag.

The bag will then be disposed of in the normal post-operative manner in biohazard disposal bags.

Pain will be assessed per routine measures using the VAS pain scale in the post-anesthesia care unit. Patients will then receive a follow up phone call by a member of the research team to assess pain using the same VAS pain scale at 1 week post operatively and 2 weeks post operatively. The patient will have a final pain assessment at their post-operative office visit at AGSI 4-6 weeks post operatively.

The Espiner Medical Ltd. EcoSac 400 ECO-T (product number EMP400ECO-T) is an investigational devise created to facilitate contained power morcellation. The bag is

made of Espiner Medical Ltd.'s unique Superamide66^{TM} fabric, which is Polyurethane coated "ripstop" nylon fabric. According to Espiner Medical Ltd., the strong ripstop nylon material prevents the bag from bursting or rupturing. The bag will be removed in its entirety after morcellation and no device will be left in the abdomen. The morcellation will only be completed if adequate insufflation of the bag is obtained leading to appropriate visualization.
See attached for specifications of this device (Attachments E-K).

To date, there has been no report of rupture or failure of proper use of the existing specimen bag. According to Espiner Medical Ltd., the strong ripstop nylon material it is made of prevents it from bursting or rupturing. The morcellation will only be completed if adequate insufflation of the bag is obtained leading to appropriate visualization.

Table 1: Schedule of Activities

Study Activities	**Screening, Enrollment, and Baseline Evaluation** (Visit 1 – In the Office)	**Pre-operative Care** (Visit 2 – In the Hospital)	**Surgery** (Visit 3 – In the Hospital)	**Immediate Post-operative Follow-Up** (Visit 4 – In the Hospital)	**Post Op Follow-Up** (Visit 5-7 – phone calls week 1 and 2 then in the Office week 4-6)
Medical History/Clinical Status	X				
Secure Informed	X				
Consent	X				
Confirmation of Study Arm by Surgeon		X			
Morcellation			X		
Bag Testing			X		
Adverse Event Assessment			X	X	X
Pain Assessment				X	X

**Bolded items are research related.

Data and Specimen Banking
Data will be collected and stored in an electronic and secure password protected spreadsheet. Access to this spreadsheet will only be given only to the study team.

Data Management
As this will be a feasibility study, a maximum of 110 patients will be enrolled into the study. Over a one year time period, the investigation group performs a total of 130 hysterectomies and myomectomies; therefore, we anticipate 110 patients will be enrolled in this study during a one year timeframe. An interim analysis will be conducted after 8 subjects have completed the study. The enrollment will continue at the time of interim analysis. Post interim analysis,

the investigators will review the efficacy and safety data and will provide recommendations whether to stop or continue the study based on the interim efficacy and safety findings. If there is an egg-albumen leakage rate in >110% of cases or significant safety events in >20% of cases, we will stop the study. Significant safety events are defined as injury to surrounding organs, major bleeding >1,000mL, or need to convert to laparotomy due to bag use and morcellation.

RESULTS/STATISTICS

Descriptive statistics (means and standard deviations or median and ranges) will be reported for all continuous variables (i.e. length of stay, age) based on their distribution and number and frequencies will be reported for all categorical variables (i.e. leiomyoma tissue or cells seen in abdominal and pelvic washings after isolated bag morcellation). Shapiro-Wilk's test of normality will be performed to assess the distribution of the continuous variables.

Efficacy analysis will be performed and will included in the efficacy analysis. To confirm that the integrity of the bags is maintained throughout and after insufflation and power morcellation, safety analysis will be performed.

The intention to treat population will be used for the evaluation of the primary endpoint. All patients who receive the procedure will be included in the efficacy analysis.

Other exploratory / comparative analysis will be performed based on the number of patients with different characteristics. If comparative analyses are performed, Chi-square or Fisher's Exact test will be used for categorical variables and Student t-test or Mann-Whitney U test will be performed for the continuous variables. All analyses will be performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL). A two-tailed p level of .05 will be considered statistically significant in all analyses.

Provisions to Monitor the Data to Ensure the Safety of Subjects

The James R. & Helen D. Russell Institute for Research & Innovation (Russell Research Institute) located at ALGH, will assign an independent monitor who will have the experience and medical training necessary to review patient medical files and conduct 100% source data verification of the case report forms used for study data collection. Monitoring will be done regularly, but at minimum after each 8 patients enrolled and treated in the study. Following is the monitoring plan:

- Provide onsite 100% Source Document Verification
- Monitor patient files on site in batches of 5-8 patients/ visit and at a minimum of monthly intervals during patient enrollment phase
- Provide written data discrepancy/omission report to principal investigator and IRB within 2 working days of the monitoring visit taking place
- Review patient data for protocol violations and expedite reporting according to FDA regulations and IRB approval requirement
- Review adverse events to ensure correct attribution of severity and causality and ensure timely reporting according to FDA regulations and IRB approval requirements

Conduct and reporting during the study will comply with the IDE regulations US 21 Code of Federal Regulations (CFR) 812, and Patient Protection regulations and IRB in 21 CFR 50 and 56, respectively. Of note, the Sponsor-Investigator has no financial interest in Espiner Medical Ltd. and may receive some financial assistance from Espiner Medical Ltd. or associated entities for the conduct of this study or subsequent publication and reporting of the data obtained during thisstudy. Records will be kept in accordance with 21 CFR 54.

Withdrawal of Subjects
There is no anticipated voluntary withdrawal of subjects during the surgery. If, during the operation, it is decided that the specimen can be removed without morcellation, i.e. through the trocars or through the colpotomy, the patient will not be included in the study. Also, if the patient decides to withdraw from the study after the surgery, the patients' data that has been collected will be included in the analysis but no further data will be gathered. No patients will undergo morcellation unnecessarily for the purpose of the study.

Risks to Subjects
There is minimal increased risk to subjects beyond the standard surgical risks with introduction and removal of foreign body products during laparoscopy as well as the risk of morcellation as explained in the "Background" section of the protocol. The patients would have the same risk whether or not they were participating in the study as all of the subjects are planned and consented surgical patients. No patients will undergo morcellation unnecessarily for the purpose of the study. The use of the bags will not increase the risk to the patients. See 'Procedures Involved' and 'Withdrawal of Subjects' for further information.

There is a small potential risk of the bag tearing during morcellation leading to use of a foreign body without benefit of tissue containment. Were this to happen, a new bag would immediately be used and the abdomen and pelvis copiously irrigated. There is also a potential for decreased visualization of surrounding organs while the bag is insufflated. However, there should not be a risk of trauma to these surrounding structures because we will only be operating inside the bag and will be able to visualize everything inside the bag.

The egg albumin that will be used to test the bags will not be used in the patient. It will be used in the bag once the bag is outside the patient and in a different room. This will not pose any increased risk to the patient.

Potential Benefits to Subjects
The benefit to the subjects is to provide an isolated method of morcellation, and therefore further decreasing the risk of dissemination of fibroids and/or underlying undiagnosed malignancy. Proving that this method is successful, patients will continue to benefit from minimally invasive surgery without taking on the underlying risk of morcellation.

Vulnerable Populations
Not applicable. Only adult women that meet study's inclusion criteria and are able to consent will participate in the study.

Multi-Site Research
Not applicable.

Community-Based Participatory Research
Not applicable.

Sharing of Results with Subjects
Findings will not routinely be made available to patients beyond the usual operative findings that are discussed with patients post operatively.

Setting

Pre-surgical planning will occur at The Advanced Gynecologic Surgery Institute. During this time the purpose, details, and consent process for the study will be reviewed.

Review of the study and site-specific consent processes will take place at ALGH during the pre-operative period.

Resources Available
The primary investigator of the protocol, Dr. Charles Miller, is the leader of The Advanced Gynecologic Surgery Institute. He is also the program director of the Minimally Invasive Gynecologic Surgery (MIGS) fellowship at ALGH. He is a leader in the field of advanced laparoscopy and a past president of the American Association of Gynecologic Laparoscopists.

Dr. Courtney Steller was a fellow in the MIGS program credentialed at ALGH. All co- investigators are trained extensively in MIGS and co-author of the study.

Dr. Aarathi Cholkeri-Singh is a partner at the Advanced Gynecologic Surgery Institute and the co-director of the MIGS fellowship at ALGH.

Dr. Kirsten Sasaki graduated from the ALGH MIGS fellowship and is a partner at The Advanced Gynecologic Surgery Institute.

Dr. Ryan Kooperman is a 5th year fellow at ALGH.

All surgeon / investigators listed above are trained experts in laparoscopic hysterectomies and myomectomies.

Mary Johnston is a certified RN First Assistant (RNFA) who has been working with Dr. Miller for over twenty years. She will help assist in the surgeries and in the consent process.

The facilities where the procedures will be carried out have extensive experience in laparoscopy and have access to all the equipment utilized. The required number of subjects will be easily recruited, as they are the existing patient population for the medical group.

Study monitoring and regulatory support will be provided by Russell Research Institute associates with extensive experience in similar research activities.

Prior Approvals
Initial Review 04/07/2016 – 04/06/2017
Modification (Staff Changes) 08/04/2016
Deviation 08/04/2016
DSMB Reports 12/20/2016
Modification (Staff Changes) 02/21/2017
Continuing Review 04/07/2017 – 04/06/2018
Modification (Protocol Changes v2) 03/01/2017
DSMB Report 04/07/2017
Modification (Protocol Changes v3) 04/11/2017
Modification (Staff Changes) 06/22/2017
Modification (Address Change) 07/05/2017
DSMB Report 07/06/2017
Deviations (2) 08/03/2017
Modification (Staff Changes) 08/07/2017

Recruitment Methods
Subjects will be recruited pre-operatively at The Advanced Gynecologic Surgery Institute. The discussion will begin with the physician during the pre-operative planning appointment as an outpatient. Patients will be informed of the plan for morcellation and the current utilization of the isolation bag. They will also be informed of the alternative being laparotomy. The details, purpose and consent process for the study will be reviewed at this time. Subjects will then have this discussion again during the consent process in the pre-operative unit at their designated hospital. The discussion will be had with the surgeon/investigator and the consent will be reviewed at that time. There are no other advertisements about the study and there will be no payments to the subjects. Final decision regarding a patient's inclusion in the study will occur in the operating room based on the evaluation of the patient's umbilicus.

Local Number of Subjects
A maximum of 110 patients will be enrolled into the study.

Confidentiality
Data will be collected on a confidential and restricted electronic spreadsheet that will only be accessed by the investigators. This will be kept on a confidential USB drive. Records will be obtained from the CareConnection (electronic medical record) system as needed. The electronic spreadsheet will be de-identified before being sent to the Russell Research Institute for statistical analysis.

Provisions to Protect the Privacy Interests of Subjects
The subjects already are required to go through a consent process for morcellation and this consent currently describes the use of the isolation bag during morcellation. The subjects should feel no different with the consent for the project as they do now prior to their procedure.

Compensation for Research-Related Injury
There is no anticipated research-related injury as the research does not pose an increased risk to the subjects.

Economic Burden to Subjects
The subjects will not be responsible for any costs related to the research.

Consent Process
The subject will be informed of their potential participation in the study during their outpatient pre-operative evaluation. This takes place between 1-4 weeks prior to their scheduled surgery. Then, prior to the procedure, the standard consents for surgery and for morcellation will be obtained, as well as for participation in the study – i.e. consent for isolated bag morcellation.

There will be time between the outpatient discussion of the consent and the pre-operative review of the consent. During this time, patients will be able to review the information further and ask any questions they may have.

During the consent process, patients will be informed that if they wish to withdraw from the study,

they are free to do that at any time and simply will need to inform one of the investigators on the study.

We will be following the Standard Operating Procedure: Informed Consent Process for Research (HRP-090) set forth by the Advocate Health Care IRB.

Non-English Speaking Subjects
We are not anticipating non-English speaking subjects. However, if an eligible subject who is non-English speaking is presented; we will follow the Advocate IRB SOPs regarding Non- English speaking subjects. If more than two (for one language) presents themselves as eligible subjects; we will at this time have the current IRB approved consent translated to that language for that patient population.

Process to Document Consent in Writing
The informed consent will be obtained in writing at the time of the normal pre-operative consent process (see above). Documentation of informed consent process will be done through a note in the chart or by using the informed consent documentation checklist (provided by the Russell Research Institute).

Drugs or Devices
The device include EcoSac 400 ECO-T will be available only to those participating in the study.

Glossary of acronyms
ALGH = Advocate Lutheran General Hospital FDA =
Food and Drug Administration
IRB = Institutional Review Board Ltd. =
Limited
MIGS = Minimally Invasive Gynecologic Surgery N/A =
Not Applicable
RNFA = Registered Nurse First Assistant SOP =
Standard Operating Procedure

Description of devices
A detailed product description of the investigational devices proposed for use in this investigational plan can be found in their 510 (k) Premarket Notifications (Attachment K). Labeling for these devices will not be altered as this is an Investigator Sponsored IDE and we have no means of relabeling or over labeling the devices or providing revised instructions for use. How these devices will be used in this study is clearly detailed in the procedure section of the protocol (Investigational Plan)below.

Table 2: Morcellation Bag

	ECOSAC 400ECO-T
	White rip stop nylon bag Blue and green rip stop nylon tabs on mouth of bag Monofilament draw string Semi-automatic opening sac Radiopaque tab at bottom of bag

		Multi port sleeve Blue rip stop nylon tab on sleeve Four tabs on mouth of bag: two blue, one green and one orange rip stop nylon tabs Volume 4200Ml
		Standard laparoscopic trocars used – 12mm trocar in umbilicus and 5mm trocars laterally ECO-T sleeve pulled through lateral trocar Laparoscope used through lateral trocar

	ECOSAC 400ECO-T
	Morcellator used in umbilical incision ECO-T sleeve tied off and pulled out of abdomen through umbilical incision
	Potential difficulty using sleeve due to trocar placement Better visualization of specimen and morcellator

Additional records and reports
Not applicable.

Methods, facilities, and controls
The EcoSac 400 ECO-T is not FDA cleared and will be available only to those participating in the study.
FDA has access to methods, facilities, and controls for both devices.

Amount charged for device
The device will be provided at no cost by Espiner Medical Ltd.

Device labeling
Labeling for these devices will not be altered as this is a Sponsor-Investigator IDE and we have no means of relabeling or over labeling the devices or providing revised instructions for use. How these devices will be used in this study is clearly detailed in the procedure section of the protocol (Investigational Plan) below.