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Suture-less Trocar Site Closure Clip

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SUTURE-LESS TROCAR SITE CLOSURE CLIP

By

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SUTURE-LESS TROCAR SITE CLOSURE CLIP

Submitted By: _____

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A Thesis Approved on

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ABSTRACT

Suture-Less Trocar Site Closure for Postoperative Hernia Prevention following Laparoscopic Surgery

Hares Patel, Dr. Daniel Metzinger, Dakota Waldecker and Dr. Robert S. Keynton

Introduction: Following laparoscopic surgery, there is a need, in many cases, to close trocar sites to prevent hernias. Currently, devices that exist on the market are suture based, but the lack of standardization in the suturing techniques together with the time-consuming nature of the procedure leads to the need for improvement in trocar site closure products. Trocar closure sites do not need to be fully closed on the fascial layer; rather, sufficiently blocking the hole at the abdominal wall can significantly reduce post-operative herniation. A retrospective study on trocar site herniation (TSH) after laparoscopic surgery indicates a TSH incidence of ~5.2% out of a total of 30,568 adult and 1,098 child procedures [7]. Specifically, trocar sizes greater than 10mm, failure to suture the fascia, and fast absorbable suture were found to be linked to TSH. Thus, the purpose of this study is to present a new, rapid deployment, biodegradable device for trocar site closures.

Methods: The Trocar Site Closure Clip (TSCC) is a biodegradable clip to be inserted into the abdominal cavity through a 12mm trocar and retracted to pierce into the peritoneum and fascia. The TSCC will be inserted via an applicator through the trocar to the abdominal cavity. The trocar will be extracted from the patient. The TSCC will be pulled upward into the peritoneum and fascia. The applicator will be released leaving the

TSCC to be separated and left in the patient to seal the trocar site. The TSCC is composed of polylactic acid and tested in various manufacturing modifications for optimization. TSCC prototypes completed bench top testing in dragon skin silicone, porcine belly, cadaver, and in a chronic swine model study.

Results: The results of this study demonstrate proof of concept for a biodegradable trocar site closure clip as a potential solution as a reliable trocar site closing and postoperative hernia prevention device in laparoscopic surgery. This study shows that the biocompatible poly-lactic acid-based device can plug and seal 12mm trocar site openings along with in animal peritoneal tissue.

Conclusion: This study successfully fabricated biocompatible TSCC prototypes using commercially-available manufacturing techniques. This study demonstrated the efficacy of the TSCC to be inserted into/through a trocar and engage the abdominal wall to plug the hole and prevent postoperative herniation.

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NOMENCLATURE

TSH – Trocar Site Herniation
MIS – Minimally Invasive Surgery
LAP – Laparoscopic
TSCC – Trocar Site Closure Clip
Insertion Force – The peak force required to pass the device into the trocar
Delivery Force – The peak force required to insert the device into the medium
Retraction Force – The peak force withstood in attempts to dislodge the device out of the medium with a vertical force
CAD – Computer Aided Design
Tm – Melting Temperature

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INSTRUMENTS AND EQUIPMENT

- **BOSS Laser Cutter**
  - Model: LS1630
- **ADMET Load Frame**
  - Serial No. 7603-0905041
  - Load Cell 100lbf
  - Load Cell 25lbf
- Single Razor Blades
- **Caliper**
  - Starrett No. 120
- **Tools**
  - Hammer
  - Pliers
  - Hex Keys
  - Screw Drivers
  - Sharpie
  - Ziploc Bags
  - Scissors
  - C-Clamps
  - Screws
  - Parafilm
  - Plexiglass
  - Laparoscopic Tools
    - Forceps
    - Suture
    - Needle Drivers
    - Axillent Karl Storz Lap Tool
    - Snowden-Pencer Lap Tool
- **Ethicon Trocars**
  - ENDOPATH XCEL
    - Diameter: 12mm
    - Length: 100mm
  - ENDOPATH XCEL
    - Diameter: 5mm
    - Length: 100mm
- **FDM Printer**
  - M2 Maker Gear Printer Bot
- **Software**
  - Minitab 18
  - Solidworks 17
  - MTestQuatro

    - Adobe Illustrator
    - Microsoft Office
        - Excel
        - Word
    - Repetier-Host
        - Version 1.2.9
- **Materials**
    - PLA
        - 3D XTECH ECOMAX
    - Silicone
        - Smooth On: Dragon Skin Translucent Platinum Silicone
    - Chicken Breast
        - Simple Truth
    - Pork Belly
        - Kingsley Meats and Catering

I. INTRODUCTION

Currently, there is a need for effective/efficient trocar site closure especially with the rise of LAP surgeries to be performed with more surgeons becoming specialized, increasing technical capabilities of LAP surgery, and incentives such as lower hospitalization time or decreases risk of infection. The development of a rapidly deployed, reliable device will result in safer and faster LAP surgeries. Due to the need of a simple alternative that surgeons can rely on, a revised suture-less device was prototyped at the University of Louisville. The proposed design is inserted into the proximal end of the trocar, travels through to the distal end of the trocar to the abdominal wall where clinching arms will grip the ends of the separated tissue. The clinician will tug on the device applicator to deliver the device into the separated tissue, constricting the wound from opening and reducing the possibility of postoperative herniation. To conclude the procedure, the operator will rotate the device and snap it off the applicator. The device will be left implanted in the cavity to degrade as the wound heals.

1.2 Purpose of the Study

The purpose of this study is to continue the work off the previous student's fabrication of the device, update the manufacturing process, and verify that the newly designed trocar clip successfully closes a trocar site opening from a trocar greater than 10mm in both a cadaver and an animal.

1.3 Hypothesis

Laser cut trocar site closure devices fabricated with less than 100% fill and sharpened tips will require less insertion and delivery force compared to 3D printed trocar site closure devices.

1.4 Significance of the Study

The significance of this study is that it will develop a fast method to close trocar site wounds by minimizing the amount of time a surgeon will take in suturing the wound closed. This device is expected to decrease the incidence of TSH and evolve the current capabilities of laparoscopic surgery.

II. LITERATURE REVIEW

2.1 Clinical Problem

Minimally invasive surgery (MIS) is a modern surgical technique in which surgery is performed via 0.5-1.5cm incisions in the abdominal, pelvic, or chest cavity (Figure 1). The cavity is inflated with carbon dioxide gas and illuminated with a laparoscopic camera. Surgery is executed by the insertion of tools into the anatomical opening monitored by the camera. The most evident advantages for patients of MIS include: minimized trauma to the abdominal wall, faster convalescence, reduced hospital stay, faster return to normal activity, decreased post-operative pain, reduced risk of hemorrhaging, and reduced exposure of internal organs. MIS has continuously developed and advanced from a minimally invasive diagnostic tool to an efficient instrument for surgical treatment of benign and malignant diseases. The ongoing training, experience, and development in imaging and laparoscopic instruments have facilitated extension of the applications of laparoscopic surgery. The outcome, efficiency, decreased incidence of wound infections, and reduced perioperative morbidity of minimally invasive procedures have been shown across different applications, *e.g*., appendectomy, cholecystectomy, esophageal surgery, reflux surgery, gastric surgery, colorectal surgery, colon cancer, rectal surgery, rectal cancer, liver surgery, pancreatic surgery, splenectomy, hernia repair, and adrenalectomy [6]

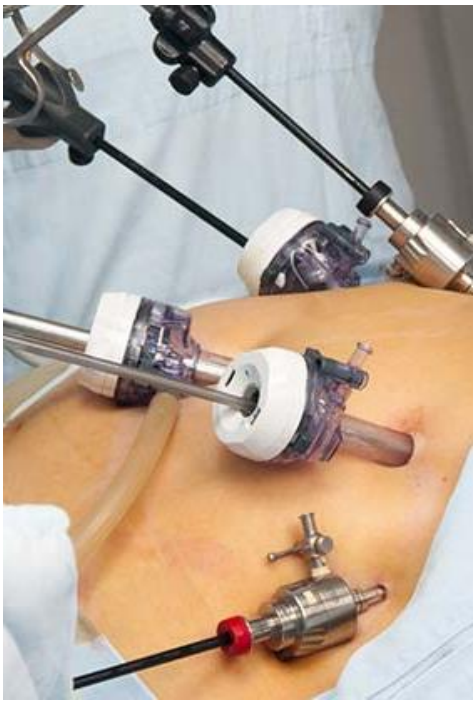


Figure 1: Depiction of laparoscopic tools being used in a MIS procedure within the abdominal cavity. [19]

The MIS technique has attained progressive global popularity over time with complex procedures. In 2013, there were 2.5 million MIS/laparoscopic (LAP) surgical procedures performed in the U.S. alone. The ports utilized to insert surgical instruments into the inflated cavity in laparoscopic surgery are called trocars. Being the only access point for surgeons, trocars are an essential component for LAP surgery.

The use of trocars in LAP surgery have several benefits for the patient, however, also present a risk of developing trocar site herniation post-operatively. A hernia is the bulging of an organ from an abnormal opening in the body, visually depicted in Figure 2. Post-operative herniation caused by trocar site is the bulging of an organ into the opened tissue site from the retracted trocar. A retrospective study on trocar site herniation (TSH)

after laparoscopic surgery published in 2011 indicates from a total analysis of 30,568 adult procedures and 1,098 child procedures, an incidence of TSH of 0-5.2% [7]. 96% of TSH resulted from a trocar diameter of 10mm or greater and 82% of the TSH cases occurred in the umbilicus region. Blunt/cutting trocars, trocar type, procedure specificity was not found to be related to TSH. Trocar sizes greater than 10mm, failure to suture the fascia, fast absorbable suture was found to be linked to TSH. In addition to TSH, ineffective trocar suturing can be cumbersome and adds time to the surgical procedure, can be intricate, inaccurate, and requires several operators.

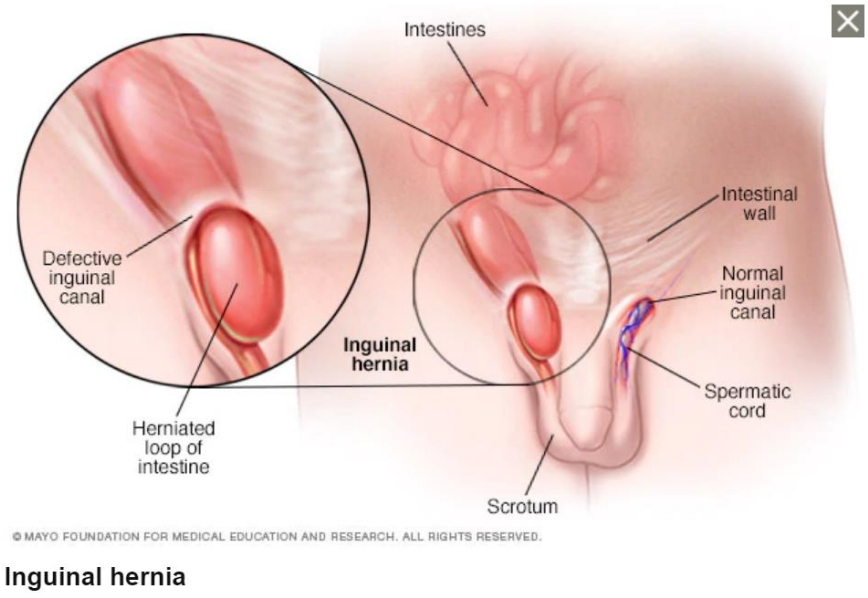


Figure 2: Anatomical depiction of an inguinal hernia.[20]

2.2 Trocar Site Closure Methods

LAP procedures are increasingly popular in modern medicine. However, even with the benefits of LAP surgery, there are technical challenges of properly closing the

trocar wound site. Trocar openings dilating the fascial wound to 10mm in adults and 5mm in children are to be closed, incorporating the peritoneum into the fascial closure, to prevent the risk of hernia formation. Closure of these wounds are difficult and not always complete due to the small opening of the skin incision. Standard techniques can be difficult and frustrating, often involving a blind closure of the fascial defect [9]. Several techniques have been developed to facilitate this fascial closure. These techniques vary from delivery systems, binding systems, application procedures, and visualization techniques. Due to the variety in trocar site closure techniques, each method presents its own pros and cons. The sections that follow describe a compilation of trocar site closure techniques developed by modern medicine.

2.1.1 Maciol Needles

Maciol needles (Figure 3) are a set of three needles used to close a trocar site: a straight needle, curved needle, and a retriever needle. The straight and curved needles are fed through the abdominal wall into the peritoneal cavity with the suture. The retriever needle is inserted into the peritoneal cavity from the other side of the trocar site. Once the suture is collected by the retriever needle, the suture is pulled through the tissue under direct laparoscopic visualization. The suture is tied within the subcutaneous tissue that incorporates the fascia and peritoneum. The suture is inspected before the exclusion of the trocar. This procedure does not require any enlargement of the skin incision. Contarini et al., studied this closure technique (Core Dynamics Inc., Jacksonville, FL) for three years without the reoccurrence of trocar hernia [1].

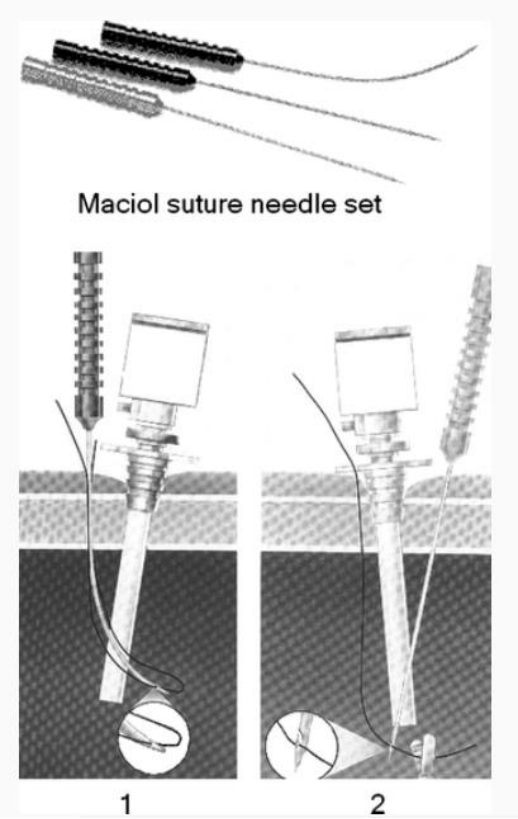


Figure 3: Graphics of Maciol suture in use.[1]

2.1.2 Grice Needle

The Grice needle technique includes the passing of one needle from opposite sides of the trocar site (Figure 4). First, the Grice needle is inserted at an angle along the side of a lateral trocar. Second the suture is passed through the fascia and peritoneum cavity. Under direct laparoscopic visualization, the suture is grasped via a surgical instrument in an opposite trocar and pulled out of the cavity. The Grice needle is removed and reinserted at an angle at the opposite of the trocar to be closed. The suture is grasped again and pulled out of the cavity. The trocar is then removed from the patient. The suture is tied with added tension placed on the site to prevent the loss of carbon dioxide (CO_2). Stringer et al. studied this technique (Ideas for Medicine Inc., Clearwater, FL) to close 80 lateral trocar sites [2].

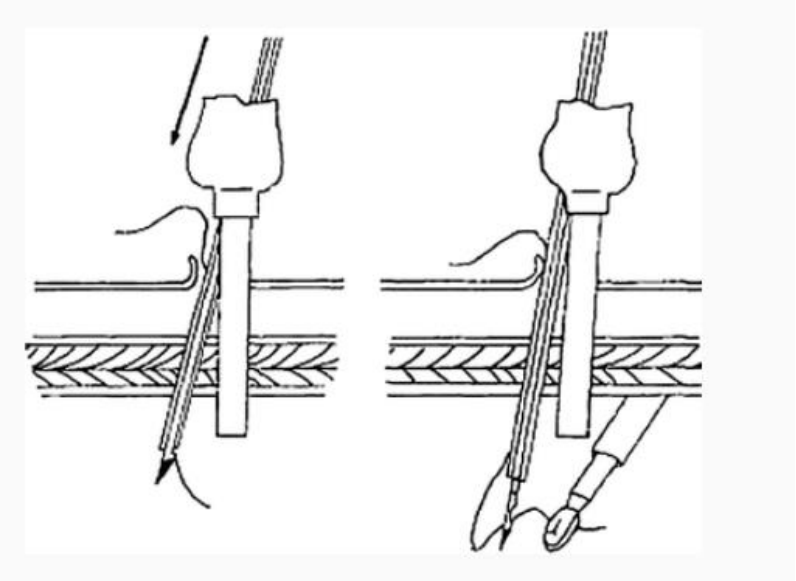


Figure 4: Graphics of Grice needles in use.[2]

2.1.3 Vein Catheter/Spinal Needle

The technique using vein catheters and spinal needles for suture placement was developed after Earle et al and Petrakis et al found a technique for closure with an o-polypropylene suture applied in a purse-string manner using a 15-gauge spinal cord needle (Figure 5). First, a nonabsorbable o-polypropylene suture is inserted with the use of a 15-gauge spinal needle 0.5 to 1 cm from the trocar site around the umbilical opening at a 45-degree angle, creating a purse string. The first needle is inserted with the suture and Endo Grasp^{TM} forceps (Medtronic, Minneapolis, MN) are used to pull the free suture edge into the abdomen. The needle holding the suture is reinserted at the next point and the free intra-abdominal edge of the suture is locked through the loop that had been created. This step is repeated three times to correctly orient the purse string. Lastly, the suture edge is pulled, and the needle is withdrawn outside the abdomen near the site of the first needle insertion, and both edges of the suture are tied up onto the fascia. This procedure was studied by Petrakis et al., however, the researchers commented “that this

method is not suitable for large abdominal wall defects, complicated hernias, recurrent hernias, or routine use to repair anterior abdominal wall defects." [2]

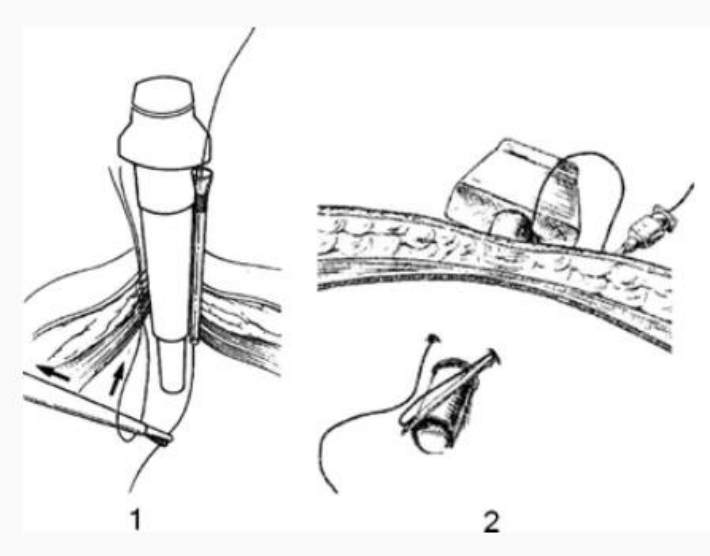


Figure 5: Graphics of Vein Catheter (left) and Spinal Needle (right). [2]

2.1.4 Endo Close Suture Device

The Endo Close™ suture device (Medtronic, Minneapolis, MN) is a spring-loaded suture carrier (Figure 6). The common technique with this device involves the loading of an o-absorbable suture. The suture is introduced to the abdominal cavity between the edge of the skin and the port via the Endo Close after which the device is removed. The Endo Close is the then injected between the edge of the skin and the port opposite to the initial insertion. The suture is reloaded into the Endo Close and the device and suture are withdrawn out of the abdomen. The trocar is removed, then the fascia and peritoneum are tied to close the tissue.

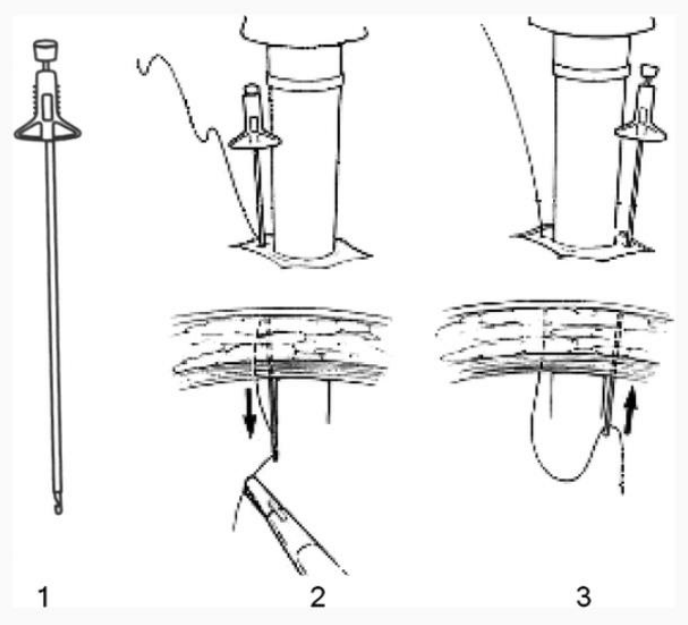


Figure 6: Graphic of the Endo Close™ suture device in use.[2]

2.1.5 Gore-Tex Suture Passer

The Gore-Tex suture passer (W.L. Gore & Associates, Phoenix, AZ) is like the Endo Close suture carrier, being a method of inserting and removing a suture from the abdominal cavity, but different because it is a reusable device (Figure 7). The Gore-Tex device is first loaded with suture and inserted into the abdominal cavity through the subcutaneous tissue and fascia on the side of the trocar to be closed (the trocar is still in place). The laparoscope is used to view the trocar site to be closed visualizing the peritoneal cavity. The suture is released from the grasper by pushing down the handle and removed from the cavity. The device is reinserted on the opposite side of the initial insertion. The suture is located, placed into the suture passer with the use of graspers in a surround trocar, and locked into position by retracting the handle. The suture is removed from the cavity by pulling the suture passer out. Lastly, the trocar is removed, and the suture is tied down [2].

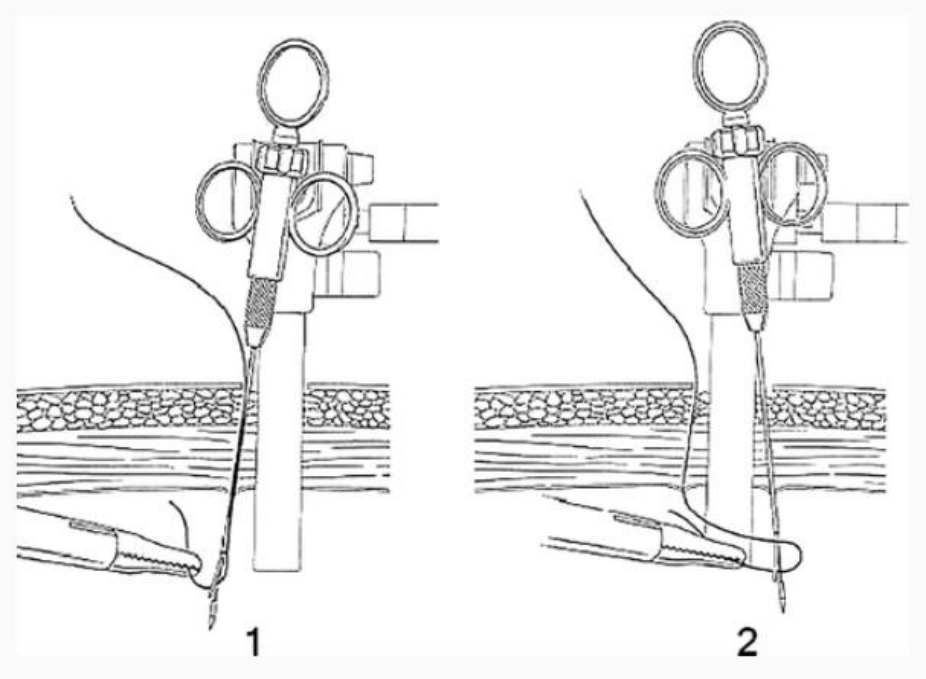


Figure 7: Depiction of the Gore-Tex Suture Passer in use. [2]

2.1.6 Carter-Thomason Device

The Carter-Thompson CloseSure System (Cooper Surgical, Trumbull, CT) consists of two components: the Pilot guide and the Carter-Thomason suture passer (Figure 8). Closure of the incision requires four easy steps. The first step includes using the suture passer to push suture material through the pilot guide, fascia, muscle, peritoneum, and into the abdominal cavity. The second step is to push the Carter-Thomason device through the opposite side of the Pilot guide and pick up the suture. The third step is to pull the suture up through the peritoneum, muscle, fascia, and guide. The fourth step is to remove the Pilot guide and tie the suture. For bariatric and obese patients, Carter-Thomason device comes in an extra-long length with a lengthened pilot guide to reach the peritoneum layer and provide full-thickness closure. Elashry et al. studied the

the CloseSure system and found that it is the fastest trocar wound closure system (~11mins) when compared to the Endo Close device and Maciol needles [2].

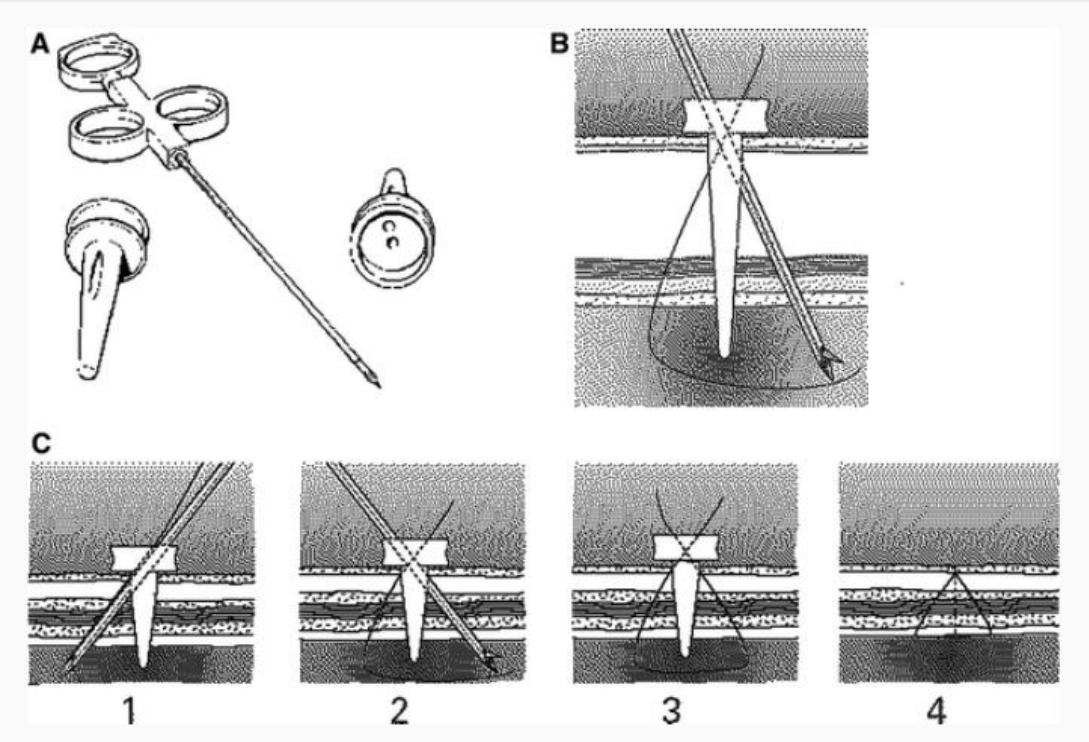


Figure 8: Depiction of how to use the Carter-Thomason device in use. [2]

2.1.7 Endo-Judge

The Endo-Judge™ (Synergistic Medical Technologies, Inc., Orlando, Florida) wound closure device is a 14-gauge hollow J-shaped needle that serves as a carrier for suture material and a device for performing the fascial closure (Figure 9). The suture is mounted on a reel at the proximal end of the device and fed to the hollow needle until it is delivered out the needle tip. The plastic oval shield (olive) at the J portion of the needle maintains pneumoperitoneum (keeps the pressure steady in the abdomen) and prevents injury to underlaying organs. The instrument is then positioned in a plane perpendicular to the trocar incision to expose the needle and pass it through the peritoneum and fascia

until it exits the skin incision. The end of the suture is grasped and tagged with a hemostat. The needle is dropped back into the olive and rotated to the opposite side. The needle is once again passed through the peritoneum and fascia via the olive. After removal of the Endo-Judge, the suture is tied creating a secure, airtight fascial and peritoneal closure. This device is used under direct visualization. [2]

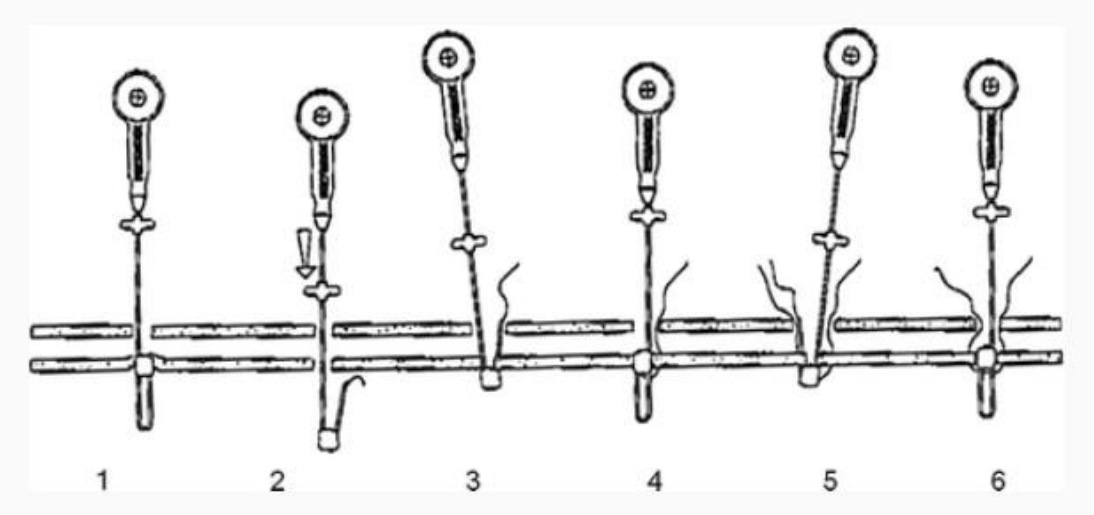


Figure 9: Step-by-step graphics of how to use the Endo Judge wound closure. [2]

2.1.8 Tahoe Surgical Instrument Ligature Device

The Tahoe surgical instrument ligature device (Tahoe Surgical Instruments (San Juan, PR) includes a handle with a locking button, one hollow metal needle for delivery and one hollow metal needle for retrieval of the suture (both ports are 2 cm apart) (Figure 10). To use this device, first the laparoscopic cannula needs to be removed. Next the suture is loaded into the hollow delivery Tahoe needle without extension beyond the distal end of the needle. The device is introduced into the abdomen proceeding the insertion of two holes on the introduction disk. The needle tips are then guided to pierce the fascia on one side of the trocar site. Releasing the lock allows the handle to depress until the metal retrieval loop is extended and encompasses the tip and distal shaft of the

delivery needle. The suture is fed into the delivery needle until it lies several inches beyond the distal end of the delivery needle and through the retrieval loop. After the handle is released allowing the retrieval loop to retract, the entire device is withdrawn from the port site. The suture is tied by the surgeon joining the peritoneum and fascia. [2]

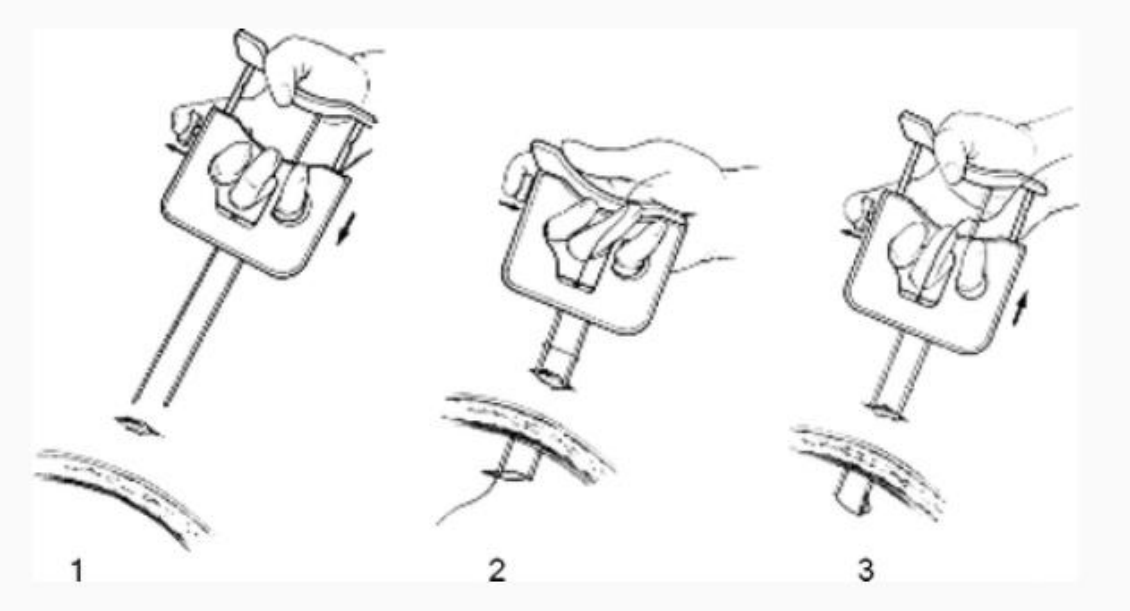


Figure 10: Graphic of Tahoe Surgical Instrument Ligature Device. [2]

2.1.9 eXit Disposable Puncture Closure Device

The eXit disposable puncture closure device (Progressive Medical, St. Louis, MO) is a 10-mm instrument with a recessed right-angle needle manually articulated from the proximal end of the device (Figure 11). Due to the size of the device, this instrument can only be used in 12-mm trocar ports. The device is inserted into a 12-mm trocar port and then needle is exposed for puncture. From the abdominal cavity, the needle is pulled up through the fascia and peritoneum. The skin is pulled away from the tip of the needle to avoid puncture of the skin. Once the needle is located out of the peritoneum and fascia, it is loaded with o-absorbable suture. The device is pushed back through the port of the abdomen with the suture. Once in the peritoneum cavity the eXit device is articulated to

the opposite side of the trocar. The needle is then pulled up delivering the suture through the peritoneum and fascia. The needle is identified, and the suture is pulled out of the device. The device is removed from the port, the trocar is removed from the site, and the suture is tied closing the post site. [2]

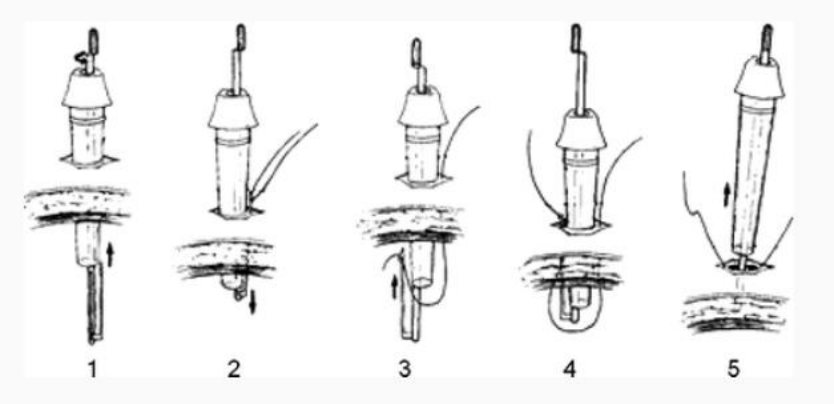


Figure 11: Graphic of eXit Disposable Punture Closure device in use. [2]

2.1.10 Suture Carrier

The suture carrier is a hooked device custom designed to maximize vertical space when accessing a trocar site for closure (Figure 12). The suture carrier is comprised of a hook retractor with an eye drilled into the tip through which suture material can be threaded. The instrument designed by Jorge et al. and Li and Chung is 24 cm long has an end effector CT needle designed by Ethicon Endo-Surgery. The procedure in using a suture carrier starts with lifting the fascial edge vertically with the hook retractor and piercing the suture carrier into the peritoneum and fascia of the wound. The suture material is threaded into the exposed eye of the carrier. Next, the suture carrier is pulled back into the abdominal cavity and pierced through the opposite side of the trocar wound site. The suture is collected and tied after the carrier is taken out of the patient. The trocar must be removed from the patient before you can perform this procedure. [3]

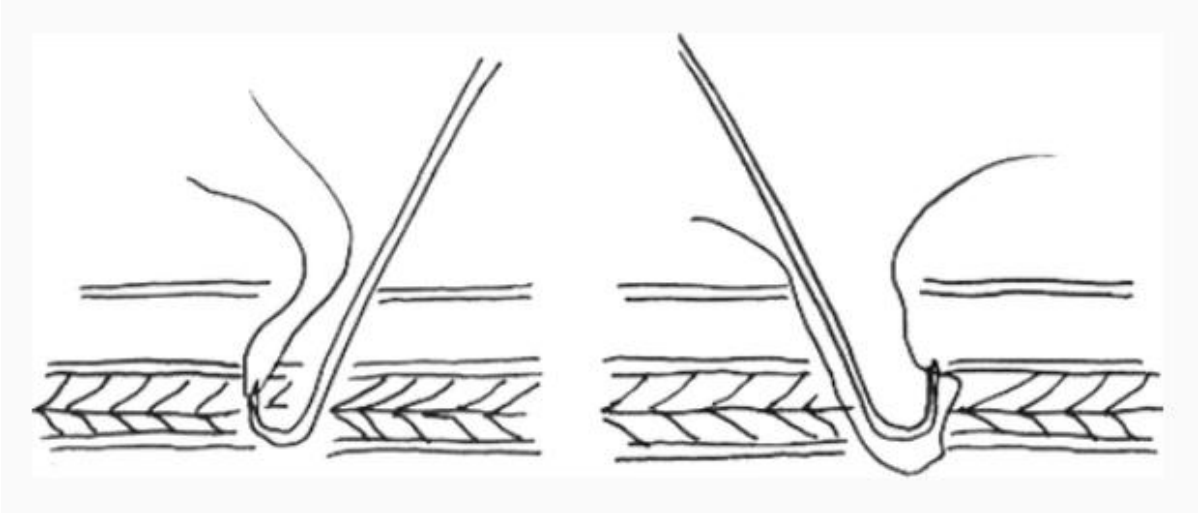


Figure 12: Graphic of the Suture carrier device in use.[3]

2.1.11 Lowsley Retractor with Hand Closure

The Lowsley retractor (Circon ACMI, Stanford, CT) with hand closure is a device for trocar site closure for wounds created by 12mm trocars (Figure 13). The Lowsley retractor is closed and slid into the intended trocar to the abdominal cavity. Next, the blades of the Lowsley device are opened and the trocar is removed from the patient. With the retractor still in the abdominal cavity and the blades splayed, the Lowsley retractor is pulled upward tilting the fascia towards the skin. A standard hand suture is then performed to close the trocar wound site.

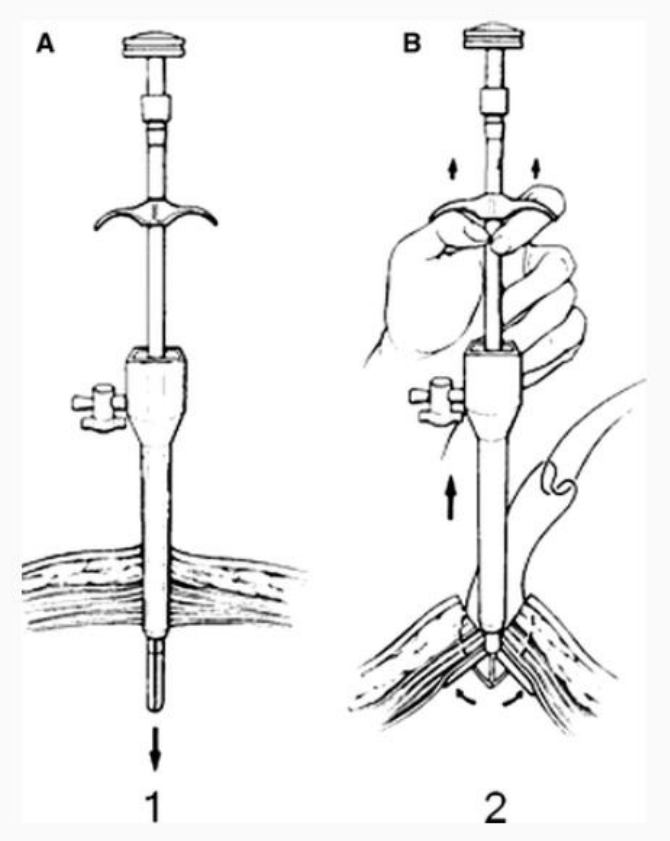


Figure 13: Graphic of the Lowsley Retractor with Hand Closure in use.[2]

2.3 Intellectual Property

A search of US Patents and Patent Applications using the terms “closure” AND “trocar” and “bio-absorbable” results in a group of 1000 matches. Another advanced search was conducted with the terms “trocar” AND “site” AND “closure” resulting in three matches. Below is a compilation of patents that propose a solution to the problem statement indicated in this study. The University of Louisville Research Foundation has secured a patent on a trocar site closure assembly reserving the intellectual property (shown at the bottom of Table 1 this study will build on.

Table 1: Table representing the hits for intellectual property search.

Patent Applications	Title	Assignee	Pub. Date
20120316594	Apparatus for closing an opening, such as a trocar opening, in a patient's body	Mount Sinai School of Medicine	12/13/2012
20110251638	Implantable biodegradable wound closure device and method	Strategic Capital, LLC	4/11/2010
8323312	Closure device	Abbott Laboratories	12/04/2012
20120022586	Tissue closure device and method	Micro Interventional Devices, Inc.	1/26/2012
20110144661	Tissue closure devices, device and systems for delivery, kits and methods therefor	CardioVascular Technologies, Inc.	6/16/2011
6939356	Medical instrument for closure of trocar site openings and method for use of same	Elle G. Debbas	9/06/2005
9451950	Apparatus and method for fascial closure device for laparoscopic trocar port site and surgery	Manoj B. Patel, Philip Zhao, Neal Patel, Landon Gilkey, David M. Albania, Salvatore Castro	9/27/2016
9463019	Trocar site closure assembly	University of Louisville Research Foundation, Inc.	10/11/2016

2.4 Literature Review Conclusion

Following laparoscopic surgery, there is a need in many cases to close the trocar sites to prevent hernias. Currently, devices that exist on the market are suture based. Lack of standardization of suturing techniques, time consuming nature of the procedure, and many different techniques to close trocar sites leads to an availability to improve closure of trocar sites. Trocar closure sites do not need to be fully closed on the fascial layer, but simply blocked at the site where the trocar penetrated the abdominal wall. By sufficiently blocking the created opening, post-operative herniation can be significantly reduced.

There are complex devices on the market that claim to close trocar incision sites, and there are suture techniques that are accepted to seal trocar wounds with cumbersome procedures. However, there is yet to be a novel device that combines an easy to use device with the reliability to prevent post-operative herniation consistently. In addition, in terms of in the realm of intellectual property, there are several opportunities to be explored.

III. METHODS & PROCEDURES

3.1 Device Characteristics

3.1.1 Specifications

The device design is a suture-less device that can be inserted through a trocar and then engaged into the tissue to block and at least partially close the wound site. Figure 15 through Figure 20 depicts a progressive conceptual example of a standard delivery mechanism for this clip device. The device will be deployed by advancing it through the trocar and possesses a flexible design so that the device can compress as it passes through the trocar. Once the suture-less device clears the bottom of the trocar, the arms spring back (or expand) to its original, non-deformed shape, the device is then pulled up into the muscle layer through the peritoneal layer. This device has two arms that engage the tissue. Each arm has anywhere from 1 to multiple barbs (2, 3, etc) on either or both sides of the arms to retain the device in the tissue while the wound heals. The device design can include stress notches on each of the arms to strengthen the device during delivery and insertion into the tissue. The device design can include retraction ribs on the outside of the arms to increase the retention strength of the clip. Figure 17 and Figure 18 depict the deformed and non-deformed state of the closure clip, respectively. This design is a U- or V-shaped to allow the arms to be flexible enough to deform through the trocar, and durable enough to withstand delivery forces. The tips and/or sides of the arms are sharpened to allow the device to tear through the peritoneal and muscle layers, reduce the

effects of tissue compliance, minimize the generation of a moment force on the device to prevent rotation during delivery, and facilitate the delivery of the device. The angular design of the barbs prevents dislocation of the device by gripping the tissue to prevent motion of the device post delivery. The devices are made of biodegradable material that will degrade as the patient heals. The porosity of the material (infill) may vary to decrease the rate of material biodegradation. The tool used to insert and deliver the trocar site closure clip can be unique to the trocar clip design or universal to fit in all endoscopic forceps. The release of the trocar site closure clip can be by torqueing, manually releasing, or snapping off the trocar site closure clip of the delivery tool. Figure 14 depicts a CAD model of a potential trocar site closure clip.

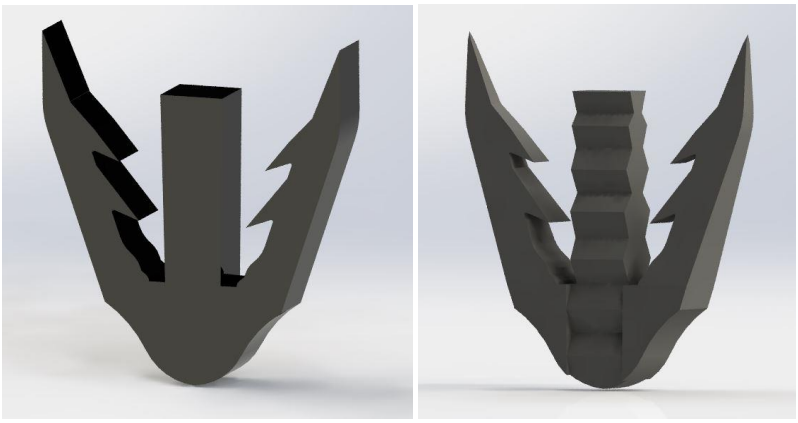


Figure 14: Solidworks Model renderings of the laser-cut device (left) and Post-processed device (right).

3.1.2 Device Delivery Concept

The order of operation for deploying the device is illustrated in Figure 15 through Figure 20, and includes the following steps:

1. Insertion of distal end of device into the proximal end of the trocar.

2. Application of axial force on the device, compressing the arms of the trocar site closure clip into the trocar.
3. Passing of the clip through the trocar into the abdominal cavity.
4. Rebound of the clip arms to the original uncompressed/non-deformed span.
5. Removal of the trocar from the patient.
6. Retraction and delivery of the trocar site closure clip to plug the trocar opening.
7. Snap or manual release of the trocar site closure clip from the delivery device.

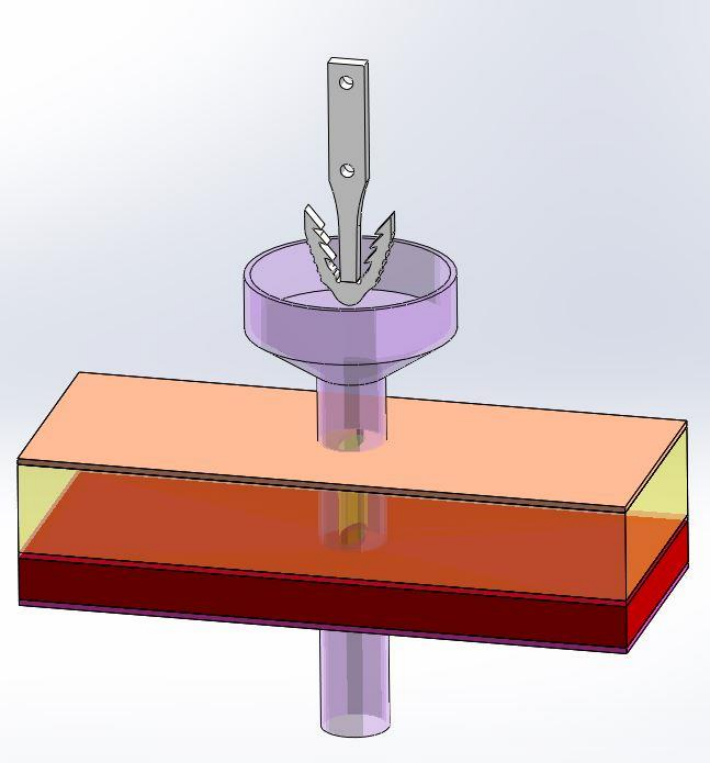


Figure 15: Insertion of the distal end of the TSCC into the proximal end of the trocar.

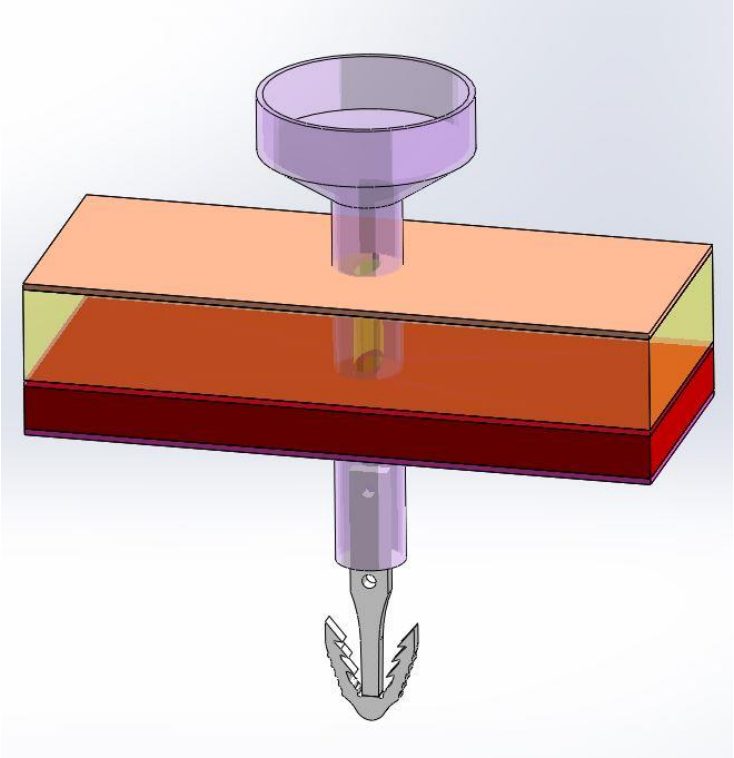


Figure 16: Passing of the clip through the trocar into the abdominal cavity.

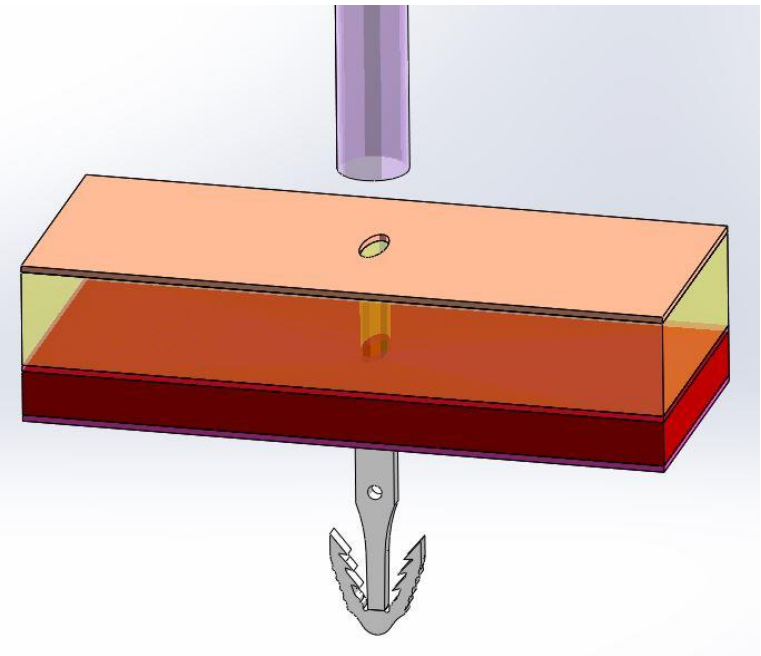


Figure 17: Removal of the trocar from the abdomen of the cavity.

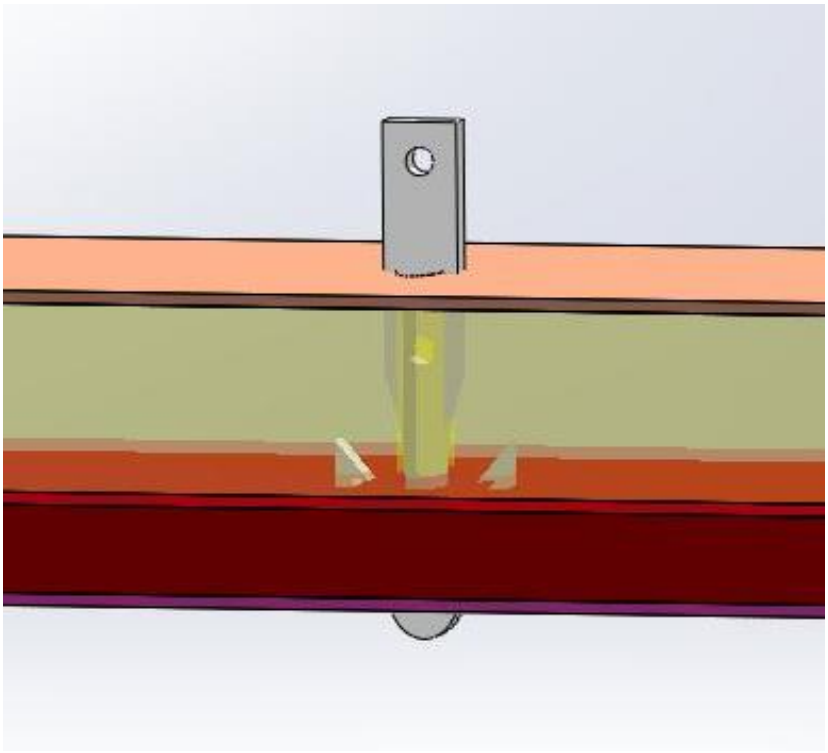


Figure 18: Retraction and delivery of the TSCC to plug the trocar opening.

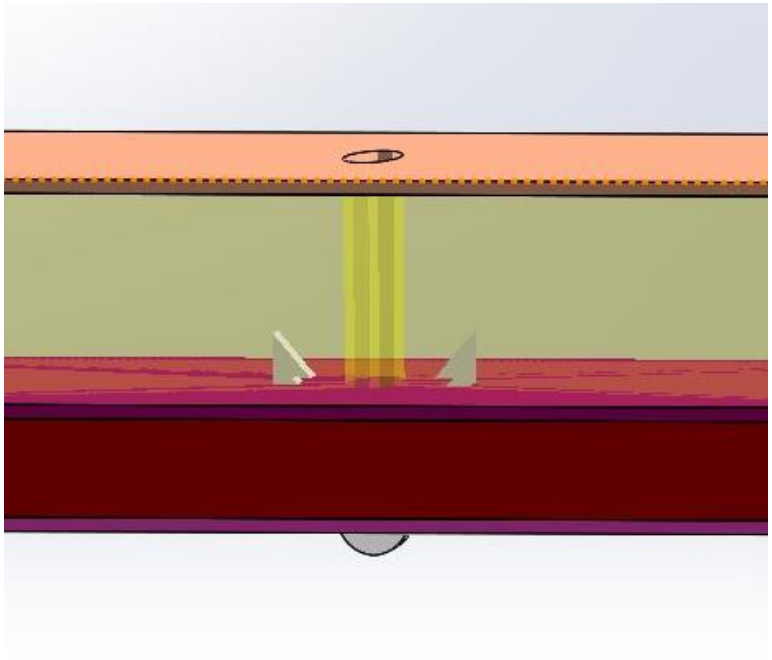


Figure 19: Remnant of device after the TSCC stem is snapped/broken off and excised.

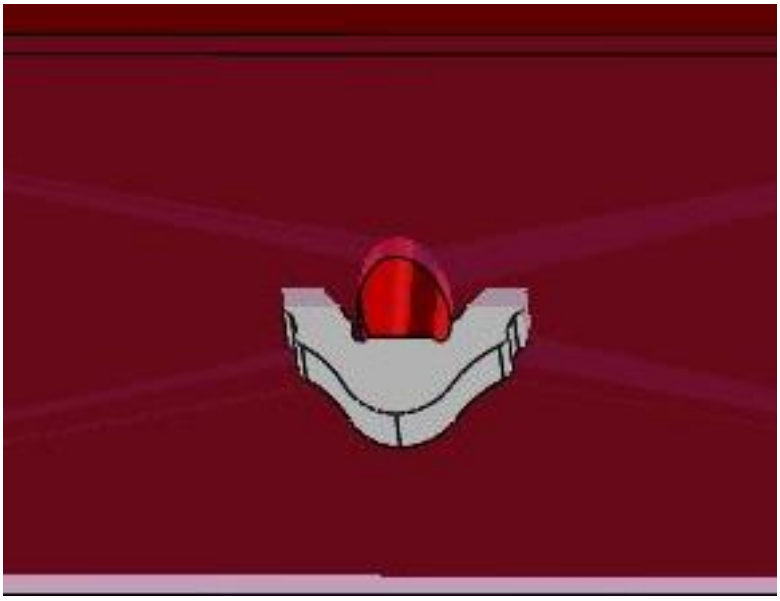


Figure 20: Bottom view of plugged trocar site.

3.2 Device Manufacturing Processes

3.2.1 Design Analysis of Distal Stem

A five design DOE was conducted with various end effectors and distal designs to optimize the distal design of the device to ability minimize the insertion force and deformation through the trocar and minimize the required force and device deformation during delivery (piercing) into the tissue. Five solid model configurations of the distal design were created in computer aided design (CAD) software (SolidWorks, Dassault Systèmes, Waltham, MA) using varying angles, notches, and narrowness (Figure 21 and Figure 22). Two thicknesses of the ABS devices (1/8” and 1/16”) were used for comparison. A full factorial study with three factors (design, thickness, and tube delivery), factors levels at five designs, two thicknesses and two tube delivery methods, along with three replicates requires a total of 60 data points. A random run order was utilized to account for device variance. Devices were constrained by an applicator at the two holes in the proximal stem of the device.

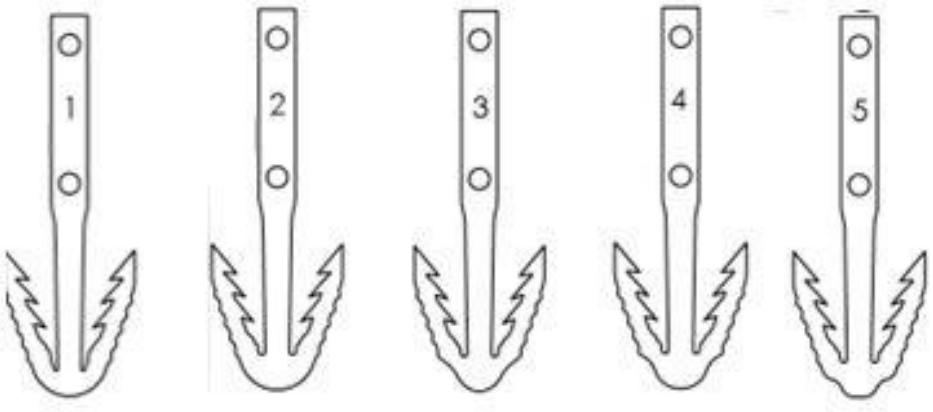


Figure 21: Different end effector designs for final design selection of ABS TSCC.

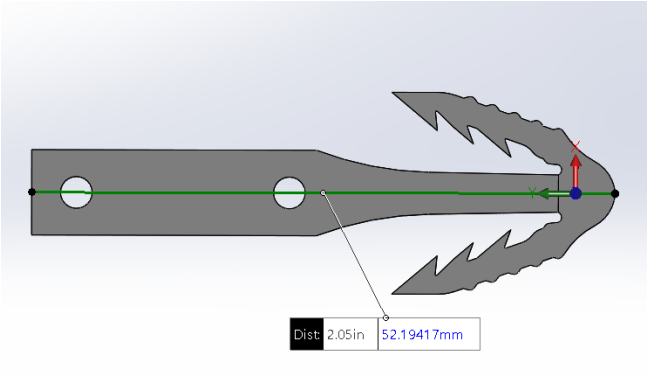


Figure 22: CAD model of Design 3.

3.2.1.1 Laser Cutter Configuration

The solid CAD model designs were transferred to an image to (Adobe Illustrator, For Web and Interactive Design, Ventura CA) cut the design onto a sheet of material. For cost effectiveness, the design study was conducted on acrylonitrile butadiene styrene (ABS), a material that is similar in tensile properties to PLA, but cheaper and easier to obtain. Devices were laser cut on a BOSS laser cutter (model: LS1630, BOSS Laser, LLC, Sanford, FL, Figure 22) and labeled for testing. For cutting, the laser cutter was programmed to cut at 20mm/s at 20% power. The laser was passed twice over the ABS sheets to ensure a clean cut of the devices. Figure 24 through Figure 29 show the general

workflow for fabricating the ABS test devices: 1) 36in by 12in sheet of ABS was placed in the laser cutter; 2) 60 devices were cut with the laser at the operating parameters stated above; and, 3) finished cut devices were removed from the laser cutter, separated and packaged based on the design and thickness of the devices.

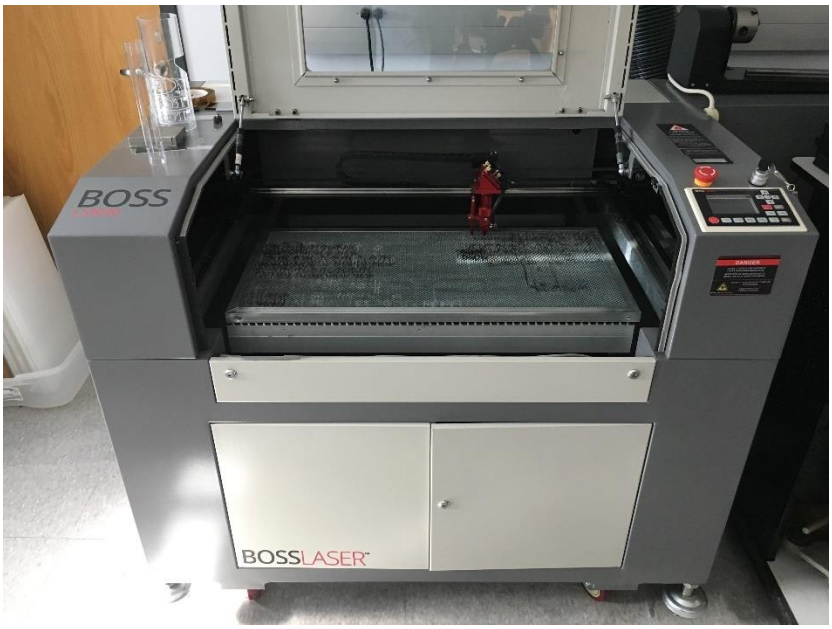


Figure 23: Laser Cutter used for device preparation.

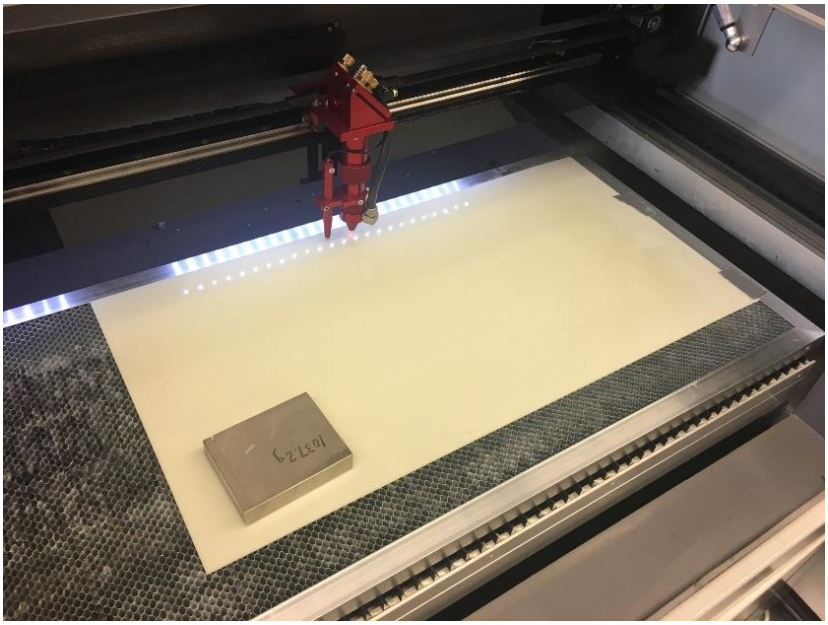


Figure 24: ABS Sheet laid in laser cutter.

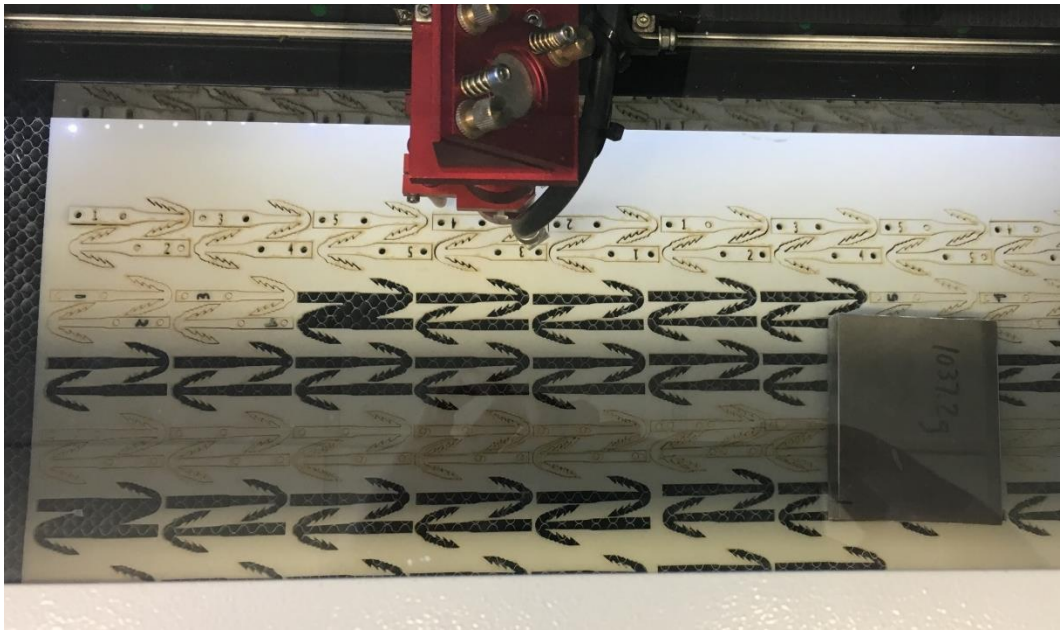
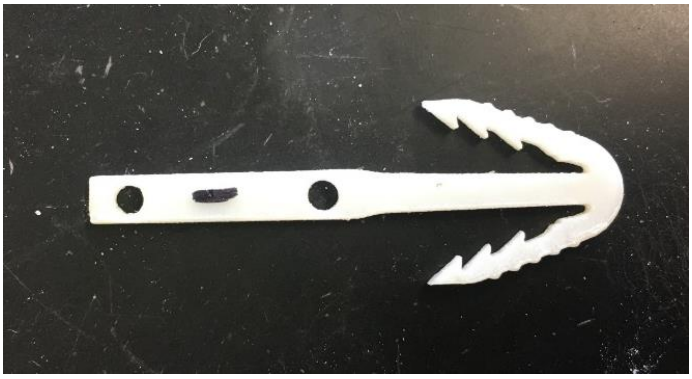


Figure 25: ABS devices being cut from ABS sheet by laser cutter.



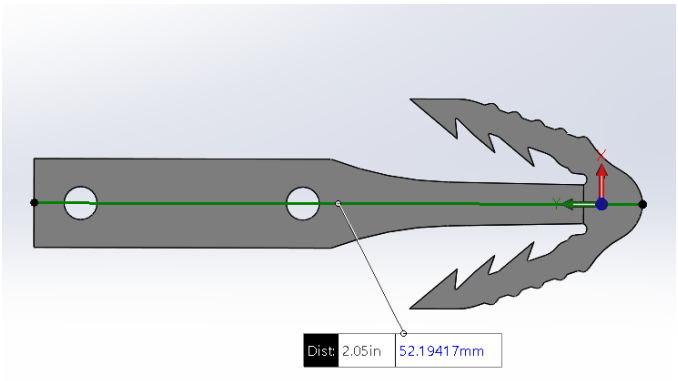


Figure 26: Finished printed TSCC from laser cutter.

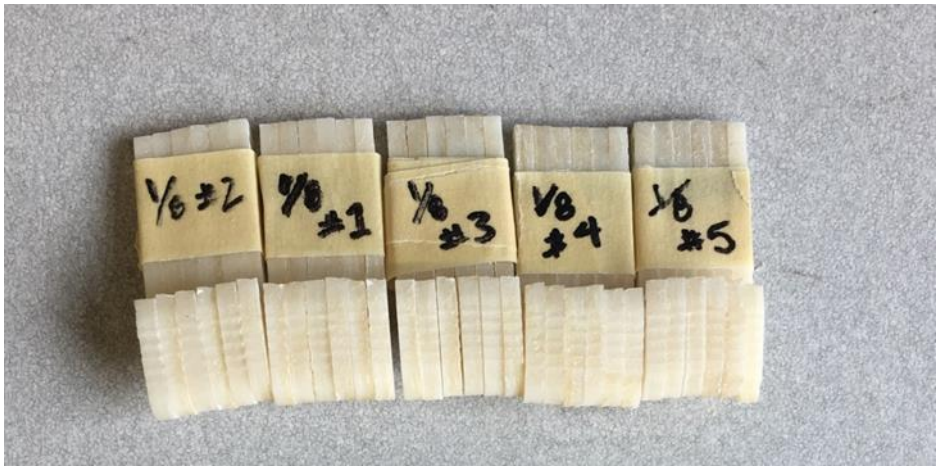


Figure 27: Finished 1/8” devices packaged and ready for testing.

Figure 28: Device applicator (top) and secured TSCC in device applicator (bottom).

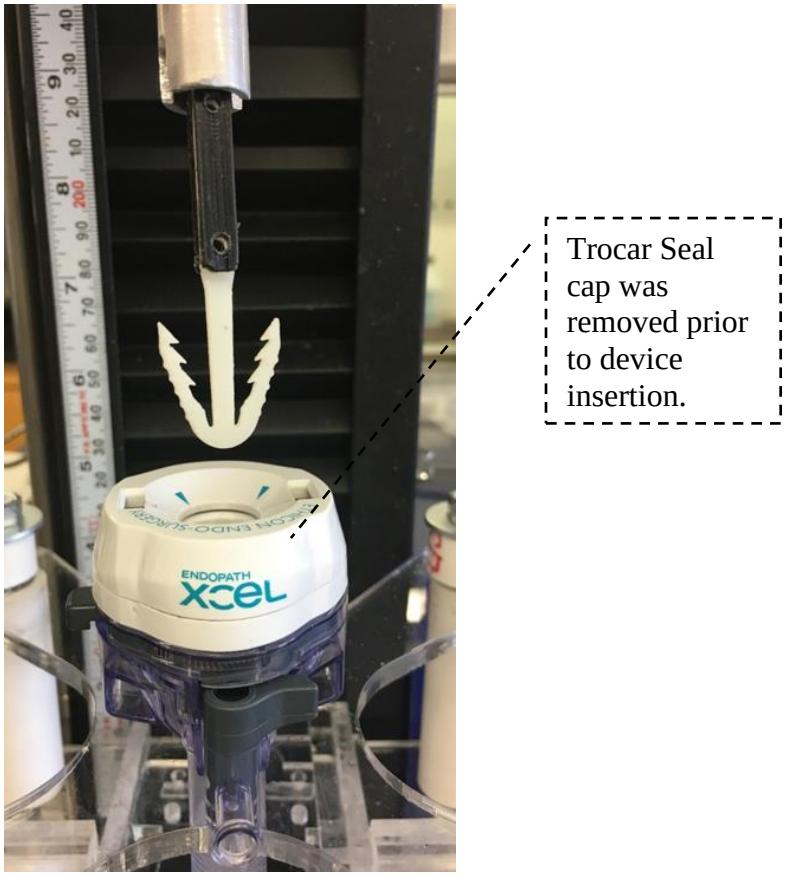


Figure 29: Line up of TSCC and proximal end of Trocar prior to testing.

The tube delivery method describes the fixtures that were used to insert and deliver the devices and the speed at which the devices were delivered into the tissue. The two speeds (tube delivery) used in this study were 1in/min and 2 in/min.

Devices will follow the order of operation described in 3.1.3 until delivery of the device onto an acrylic plate. The devices will not be tested for retraction force or the force to separate the distal end of the device from the proximal stem. A fixture was designed to orient and stabilize a 12mm trocar and allow a vertical path for the load frame.

3.2.2 Initial Device Manufacturing Process

The manufacturing process of this device started with the fused filament (3D) printing of the material. The material used in the cadaver studies was an Ecomax® PLA (polylactic acid) biodegradable co-polymer (3DXTech, Grand Rapids, MI) using 100% virgin PLA biopolymer resin and colorants. A M2 Makerbot (MarkForged, Brooklyn, NY) fused deposition modeling (FDM) printer was used to extrude an 1/8" plate of PLA to fit four devices. The PLA was printed using 100% infill which ensures a solid device. The pre-sharpened device CAD design was downloaded and then laser cut (BOSS LS-1630) in the PLA sheet printed in the fused filament printer using the same operating parameters as described above for the ABS devices. The pre-sharpened devices were then sharpened in a custom guillotine fixture (Figure 30).

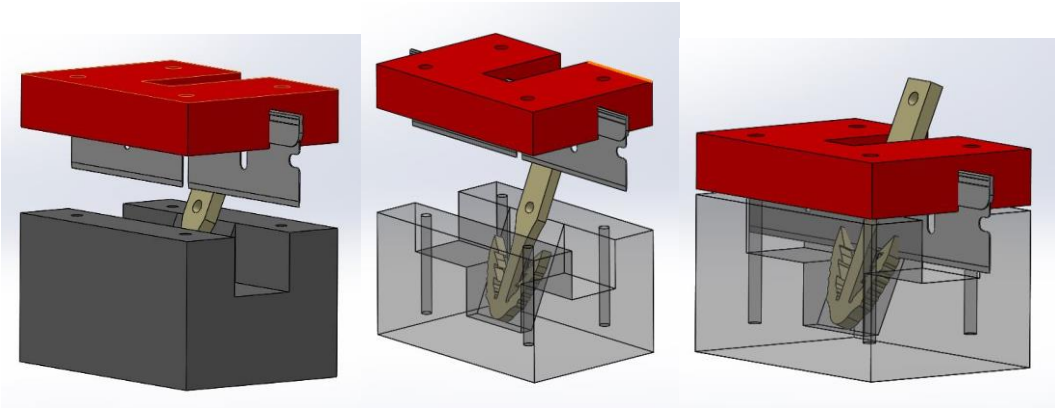


Figure 30: Process for further sharpening the tips of the device arms (left to right).

3.2.2.1 Guillotine Sharpening Method

Devices were placed in the bottom half of the fixture and a razor was placed in the top half of the fixture to create a "guillotine" type tool. The bottom half and top half of the sharpening fixture were aligned by dowel pins to drop the "guillotine" at the same location every time. The top half of the fixture was then pressed onto the TSCC mounted

in the bottom half of the fixture to cut angled corners off the TSCC arms. Once, one side of the device arm was cut, the device was flipped and cut again using the same process described above leaving sharpened tips on the device arm.

3.2.3 Modified Device/Delivery Concept

The original device delivery concept was modified from a torsional, snap-off release concept to the utilization of a separate tool to manually release the device after being delivered into tissue. Figure 31 illustrates the modified device delivery process utilizing the separate tool to deliver and release the TSCC device. This separate tool should have a long shaft length of 8in and a diameter of less than 10 mm. The tip of this tool should have a pattern on the ed effector to initiate some sort of grip on the device.

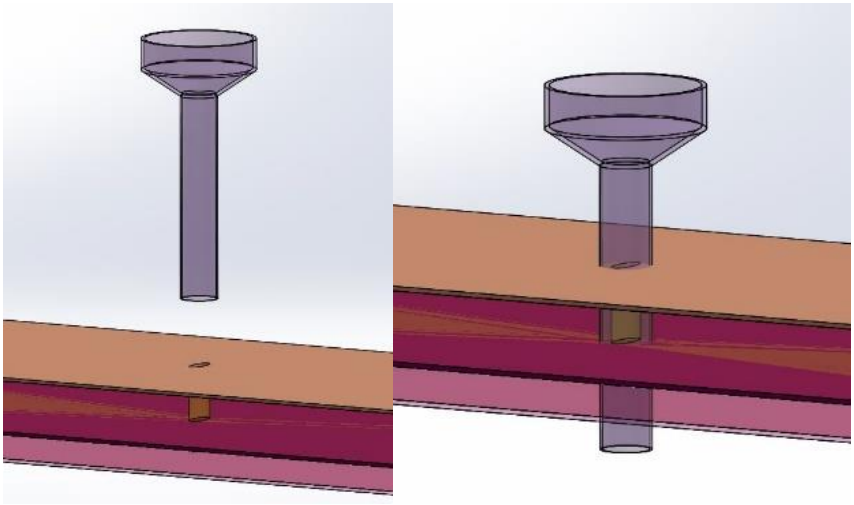


Figure 31: Schematic illustrating the insertion of the trocar into the abdominal cavity.

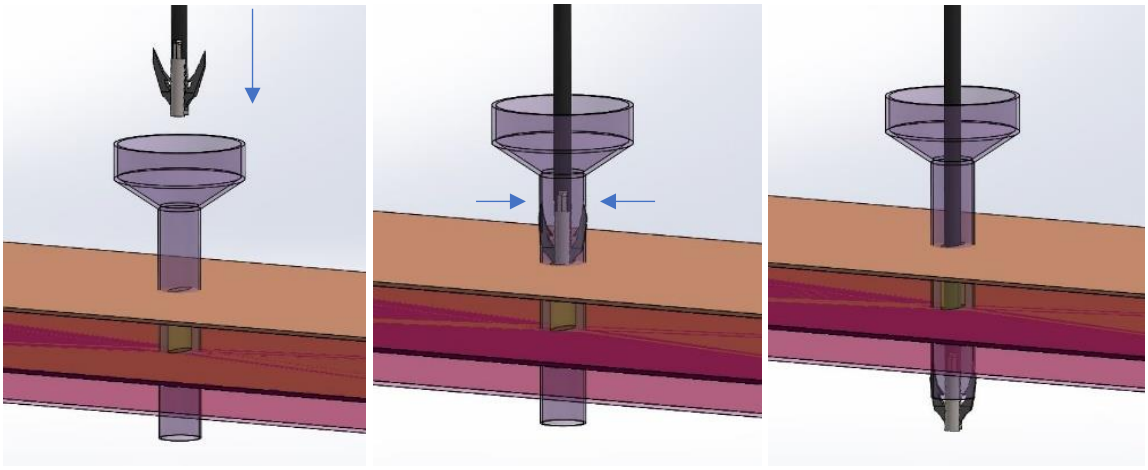


Figure 32: Schematic illustrating the compression of the device as it translates through the trocar.

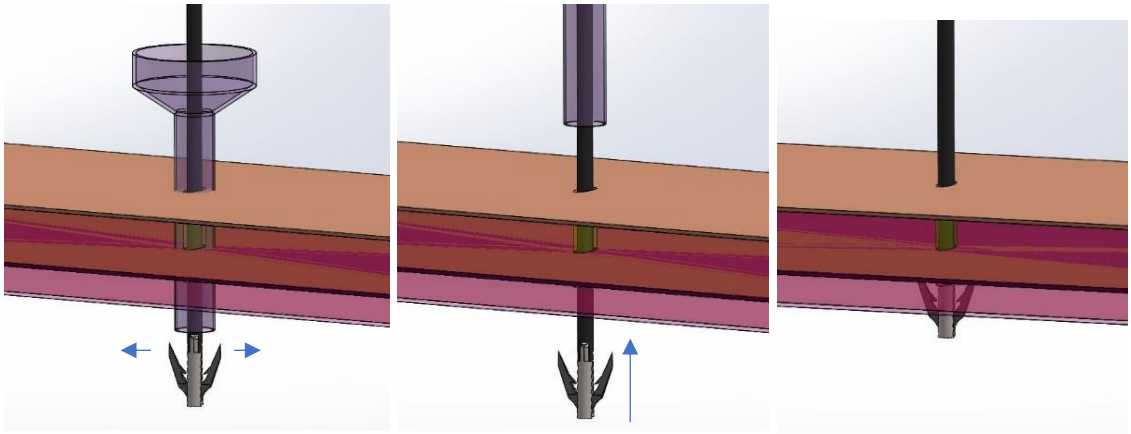


Figure 33: Schematic for illustrating the steps for removal of the trocar and retraction of the device into the fascia to plug the trocar site opening.

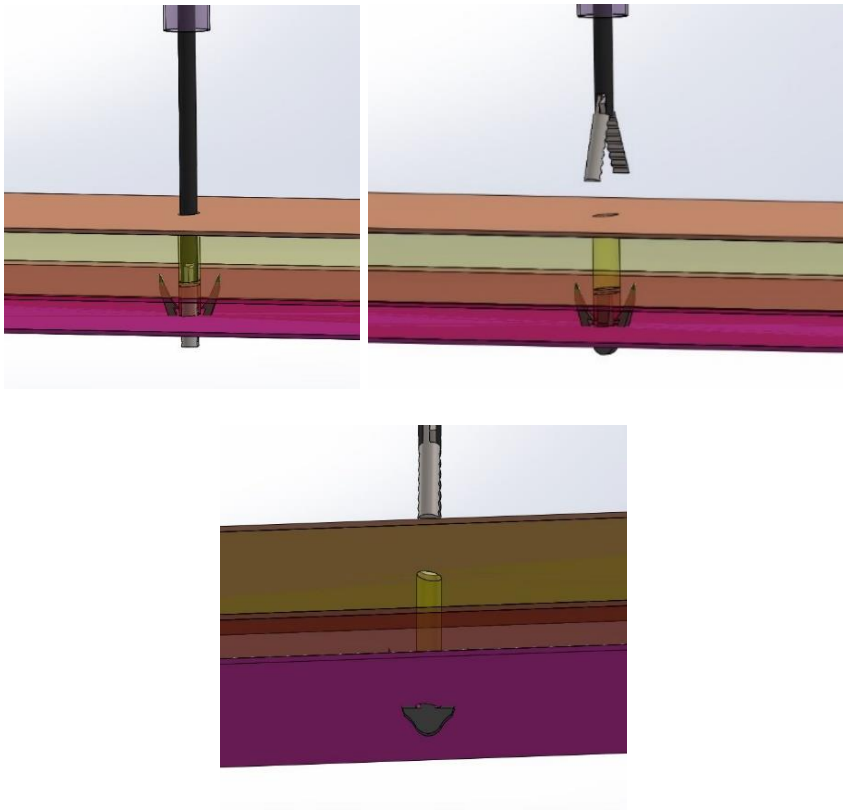


Figure 34: Schematic illustrating the release of the TSCC into the abdominal cavity to obstruct the opening.

3.2.3.1 Final Device Manufacturing/Delivery Process:

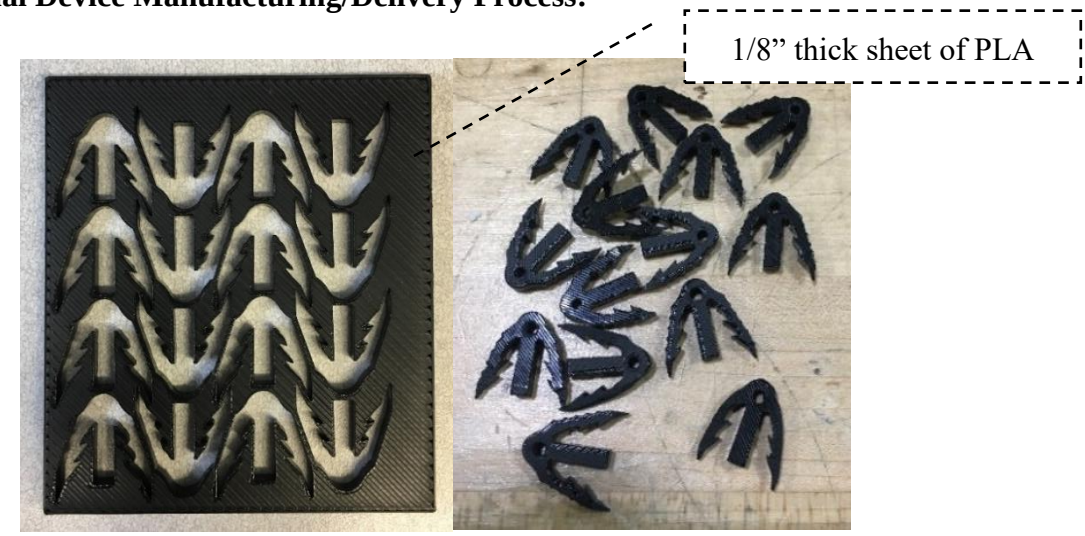


Figure 35: Laser cut devices (right) from FDM printed sheets (left) of PLA.

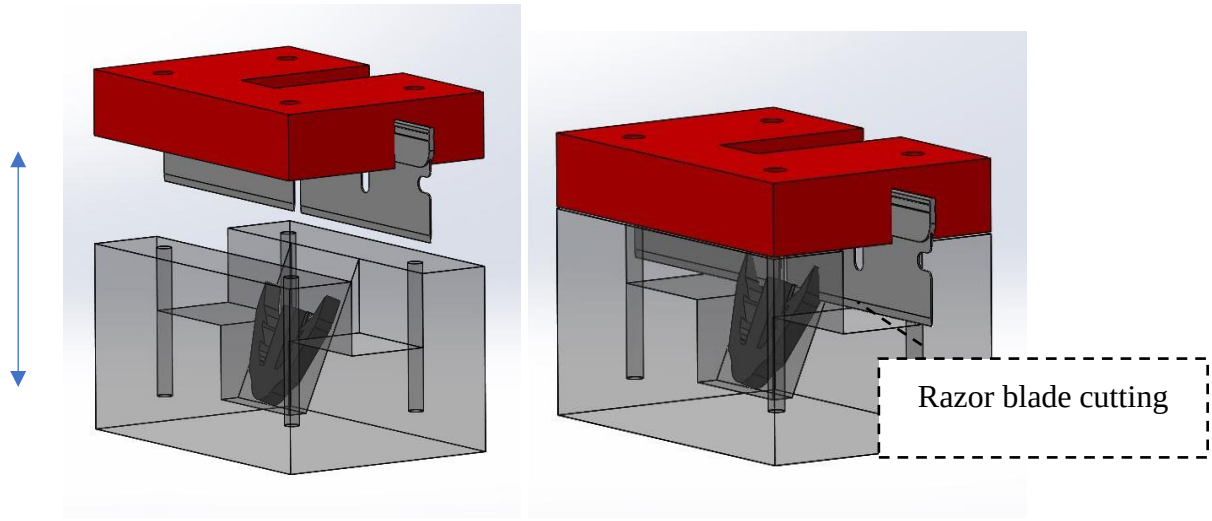


Figure 36: Schematic illustrating the guillotine fixture for sharpening tips of the new device arms.

Figure 37: Image of the Dremel tool (left) used to taper the arms of the device (right).

Figure 38: Image of device arms sanded with P220 grade sand paper for smooth finishing.

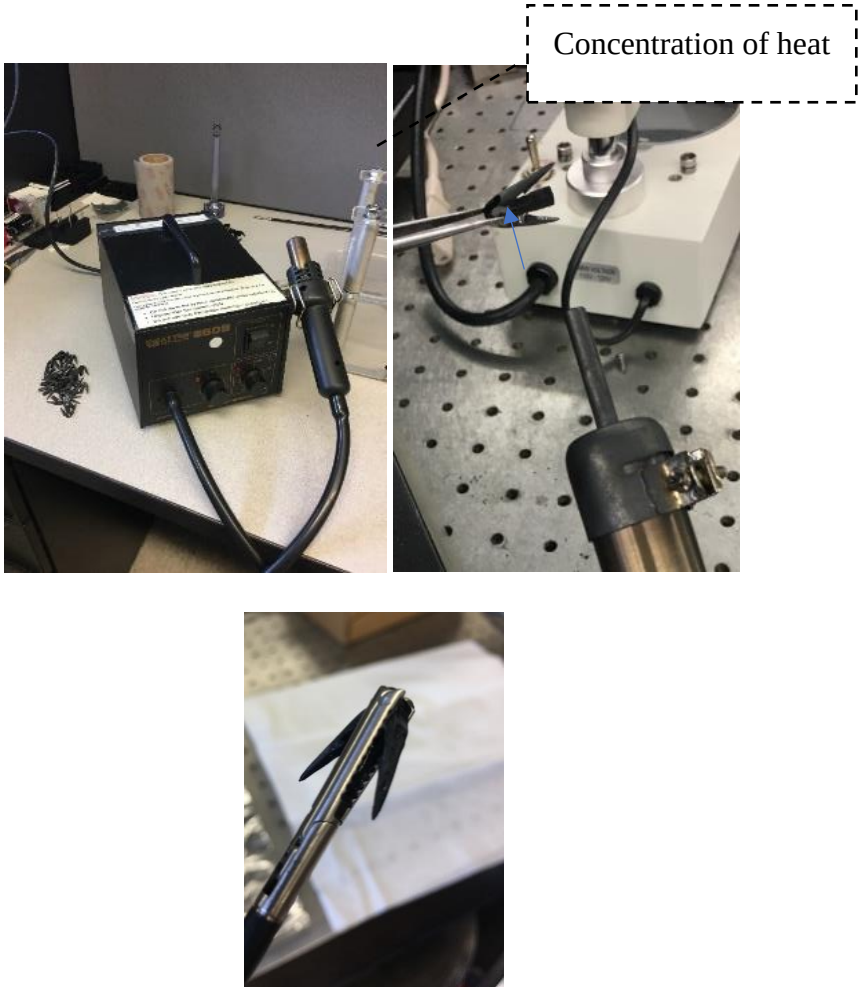


Figure 39: Images of the heating and stamping of the device stem to fix device into the endoscopic forceps. Top left: heat gun; Top right: heating of the device stem; Bottom: final device placed in endoscope forceps.

Figure 40: Final sharpening with grade P1600 sand paper of device arms: Top left: before sanding; Top right: sanding process; and, Bottom: finished device.

The manufacturing process (Figure 35 through Figure 40**Error! Reference source not found.**) of the final TSCC device started similarly to the previous method, that is, 100% virgin Ecomax® PLA biopolymer resin and colorants were used to 3D print extrude an 1/8" plate of PLA using the M2 Makerbot FDM printer. However, this

time the PLA was printed using 95% infill. The pre-sharpened device CAD design was downloaded and then laser cut (BOSS LS-1630) from the printed PLA sheet using the same operating parameters as defined above (20mm/s at 20% power). The pre-sharpened devices were inserted into the custom guillotine fixture to sharpen the tips of the device arms. The device arms were then tapered with a Dremel tool (Dremel Tools, Racine, WA) to give a triangular shape – the sharpened tip of the devices was maintained during this step. Subsequently, the arms were sanded down with two different grades of sandpaper (220-grade and 1600 grade) to decrease the surface roughness. After the device arms were sanded down to a smooth finish, the stem of the device was heated (using a heat gun Atten Instruments, 85OB) and the end effector pattern of the endoscopic forceps was stamped onto the stem of the device. A nozzle was used on the end of the heat gun to concentrate the heat on the stem of the TSCC. The heat gun was set to a temperature of 310 ºF and a blow setting of 4. The heat gun was passed over the stem at a distance of 1 inch from the TSCC device surface, twice. After stamping the devices, they were submerged in a beaker of cold water to set the mold of the TSCC design. Lastly, the 1600 grit sandpaper (3M) was used to give a vertical point to the device to improve the piercing ability of the TSCC device for tissue penetration (Figure 40). It is noted that the manufacturing process of the prototypes was constrained due to the availability of tools. This process could be greatly enhanced using more sophisticated manufacturing processes, such as injection molding, and a custom sharpening device that yields the final desired tip sharpness.

3.3 Benchtop Studies

3.3.1 Materials Testing System Set-up

A materials testing system (MTS, MtestQuatro, Norwood, MA) was used to measure the vertical forces exerted on the device as it is lowered into the trocar and as the device is pulled upward to be delivered into the tissue (Figure 42). Measurements of the insertion force and delivery force will be recorded as peak values by the MTS. The MTS was programmed with a data sampling rate of 100 Hz and recorded both the position and load force as a function to time. 100Hz was calculated using the Nyquist theory of sampling. To accurately plot the data it was estimated that 50 data points per second of load frame movement would be needed. Nyquist theory states that the frequency used to measure should be 2x $F_{max.}$ Therefore 100 Hz was used to plot the data points. 100 lb_f load cell was used to accurately measure the tensile forces. Devices were lowered and raised at a rate of 1in/min and 2 in/min to the desired distance to pass through the trocar and penetrate through the medium being tested. In this case, the medium being tested was chicken breast tissue. The chicken breasts were held down with the equal displacement of the normal force. Figure 41 shows the set-up of the load frame with the mount used to orient and stabilize the trocar. The chicken breasts were held in place by Plexiglas® around the edges. The Plexiglas® was constrained to the mount by clamps/screws. Screenshots of the MtestQuatro software is in the appendix section 6.1.

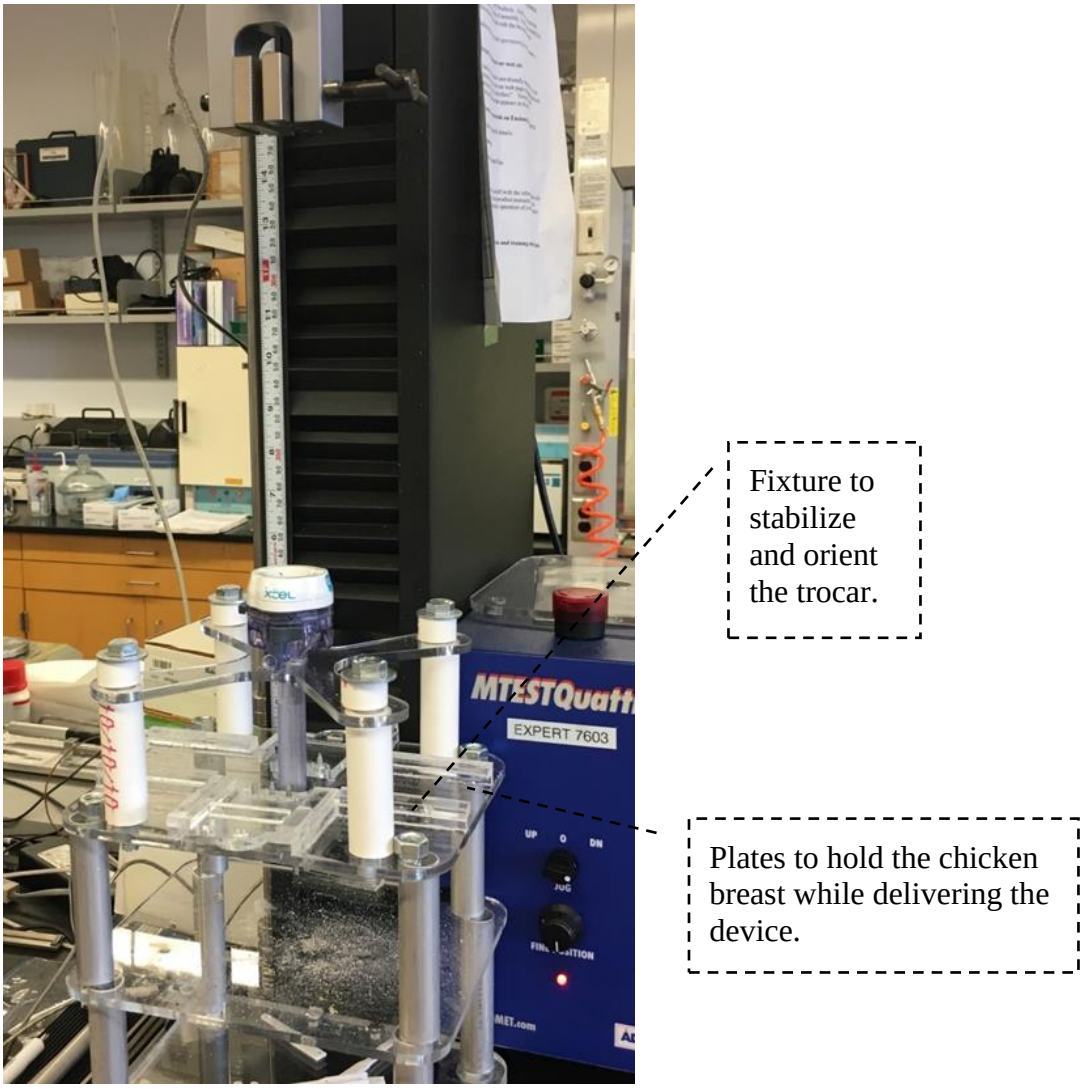


Figure 41: Image of the MTS load frame set-up used for testing the TSCC devices.

3.3.2 PLA Material/Printer Study

The purpose of this test is to compare PLA materials/printer settings to determine the difference in PLA prototype performance to be used in animal and cadaver studies. The two PLA filaments compared in this study are: 1) the PLA devices used by Dakota Waldecker (my predecessor) in his cadaver studies; and, 2) the PLA devices used in this study on cadavers. It was necessary to test this change in PLA manufacturing because the printer and filament used in the previous studies were no longer be available for this

work. Therefore, a new PLA filament and printer was compared to the previous PLA devices to determine any differences in PLA peak failure points and assess whether there were significant differences between the two prototypes. In this study, two PLA types were compared in their ability to withstand a tensile force on the arms of the device. A total of nine devices were tested from each manufacturing system.

The PLA devices used in the Cadaver Lab 1 studies were printed at Advanced Solutions Inc. using a M2 MakerGear FDM printer (Beachwood, OH). The devices used in this study were 100% infill in a 45° rectilinear pattern with a first layer extrusion temperature of 215°F and 210°F for the subsequent layers. The bed temperature for the first layer was 65°F and 60°F for the subsequent layers. The program used to splice the design was a Repetier-Host (version 1.2.9, BoXYZ, Pittsburgh, PA). Screen shots of the PLA printer settings can be found in the appendix section 6.2 of this document.

A dowel pin inserted through the proximal slot of the device stem constrained the device to the load frame. The load frame depicted in Figure 42 shows the fixture that holds the dowel pin in place while the load frame pulls the device upward. TSCC devices were compared by the peak tensile force that plastically deformed the device in tension. The two materials were tested to determine if there was a statistical difference in the material properties between the two materials used. Laser cutting of the devices followed the parameters in 3.2.2 on the PLA sheets. The load frame set up followed the parameters described in 3.3.1. The load frame head speed was 2 in/min for the upward motion of the device.

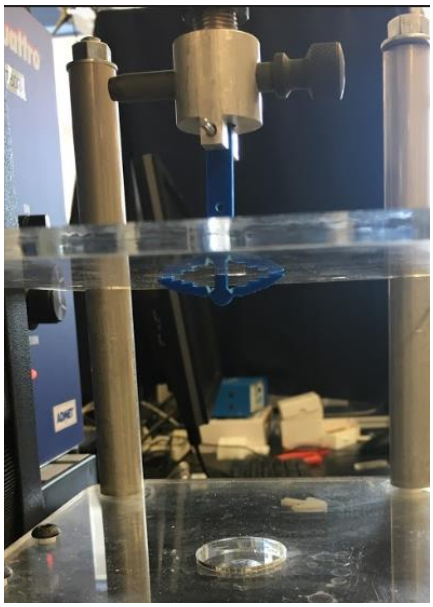


Figure 42: Test set-up for peak tensile force (constrained by dowel pin).

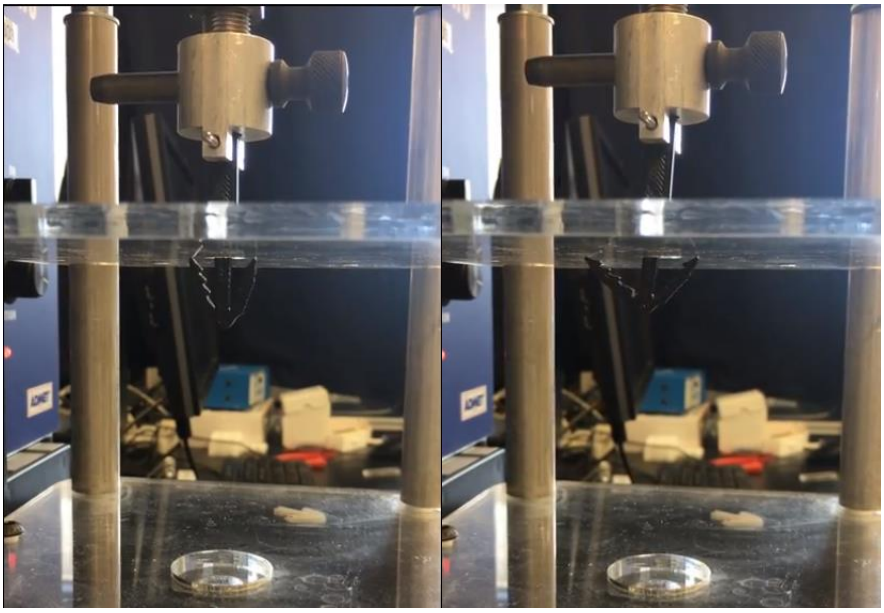


Figure 43: Before (left) and after (right) tensile force applied to determine plastic deformation peak force.

3.3.3 Infill Study

In this study, device infill was adjusted to increase the ductility of material to increase the flexibility of the device and decrease the force required to insert device into

the trocar. In addition, it was predicted that decreasing the infill and having a more porous PLA device would decrease the time for biodegradation and create pockets for tissue integration. The stiffness of the initial design created stress marks at the notches indicating that compression of the arms plastically deformed the device (Figure 44) and led to device failure during delivery of the device into the medium.

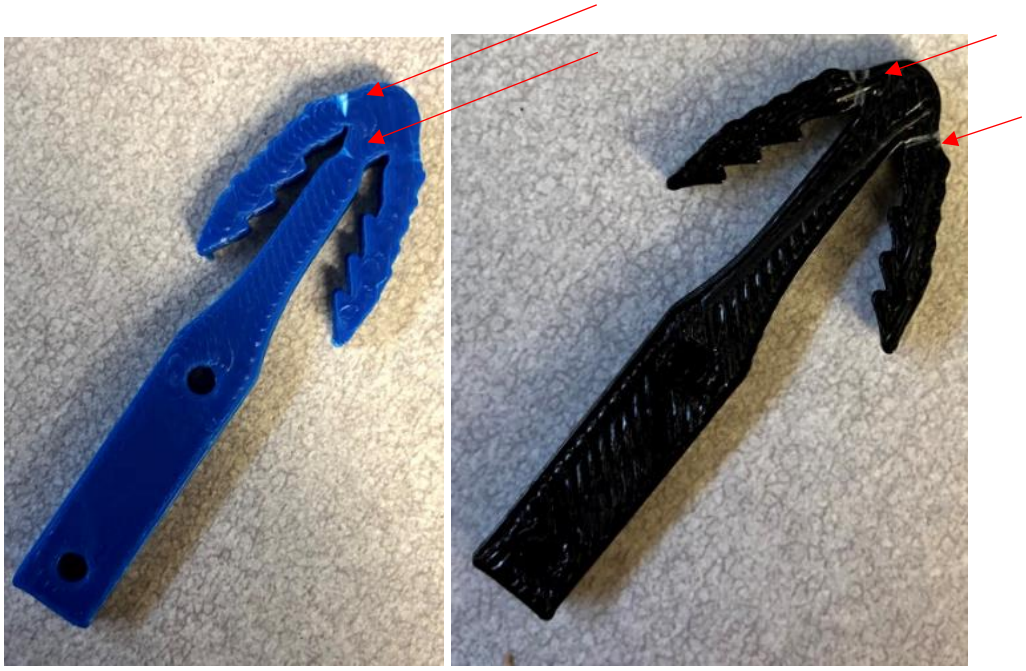


Figure 44: Depiction of the plastic deformation at the distal end from insertion into the trocar. Arrows indicate sites of stress and eventual failure of the devices.

Devices were altered to have 70%, 80%, 90%, and 100% infill during the FDM printing process of the PLA sheets. This alteration was intended to increase the flexibility of the device arms upon insertion into the trocar. The same FDM printer settings as referenced in appendix 6.2 were used, but the infill of the PLA sheets was changed to 70%, 80%, 90%, and 100%. The laser cutter and load frame settings were the same as referenced in the testing of the devices for study 3.2.2 and 3.3.1

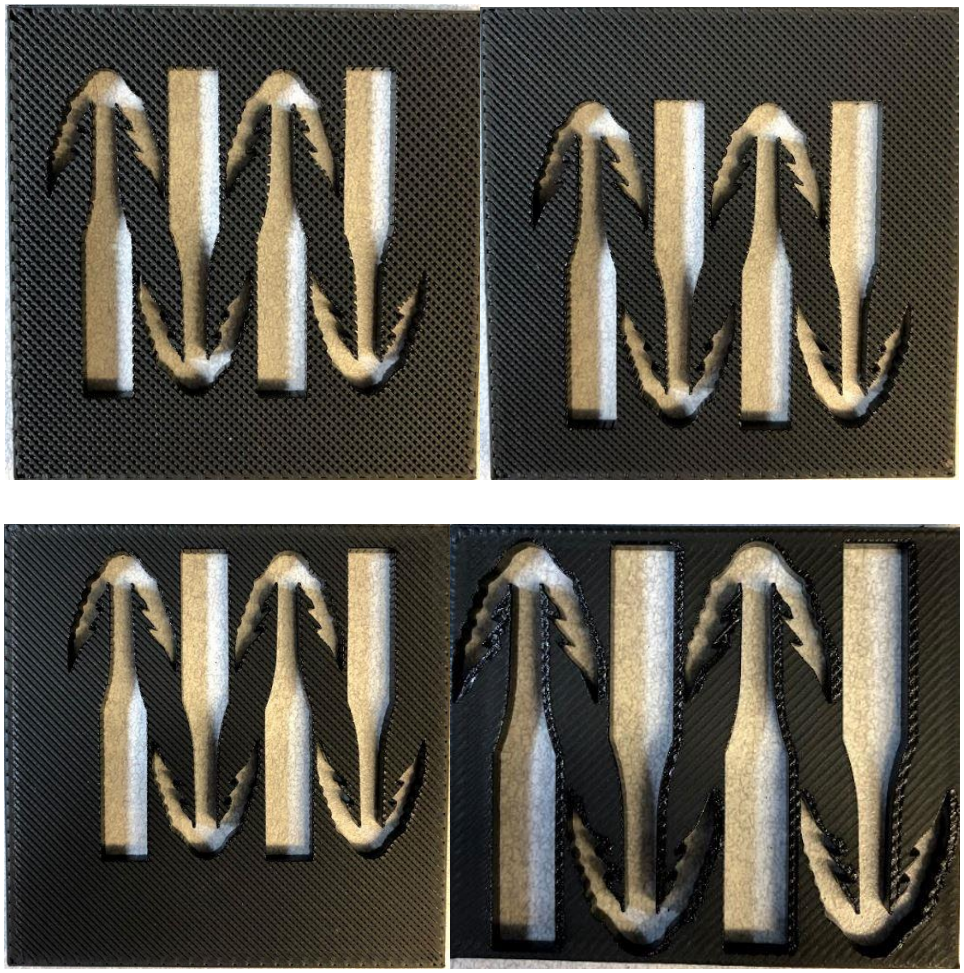


Figure 45: Images of the PLA sheet cut-outs for the varying infill settings
(top left: 70%, top right: 80%, bottom left: 90%, bottom right: 100%).

A design of experiments was created with 1 factor, 4 levels, 3 replicates, and 2 responses. The 4 levels to the infill factor were 70%, 80%, 90%, and 100% and the two responses were insertion force and delivery force. The responses were utilized to create a linear regression analysis for the optimal device infill. Comparisons were conducted in random order fashion to account for the variability of the testing procedure. Devices were inserted into a 12mm trocar to simulate the trocar that the device will be inserted during the cadaver lab. Devices were retracted into the Plexiglas® platform similar to the delivery test conducted in 3.2.2 with the same insertion rate and data acquisition settings. Figure 46 depicts the test fixture set-up for testing (similar to the testing conducted for

the design and material study 3.2.1 and 3.3.2, respectively). The devices were constrained by two set screws at the proximal stem.

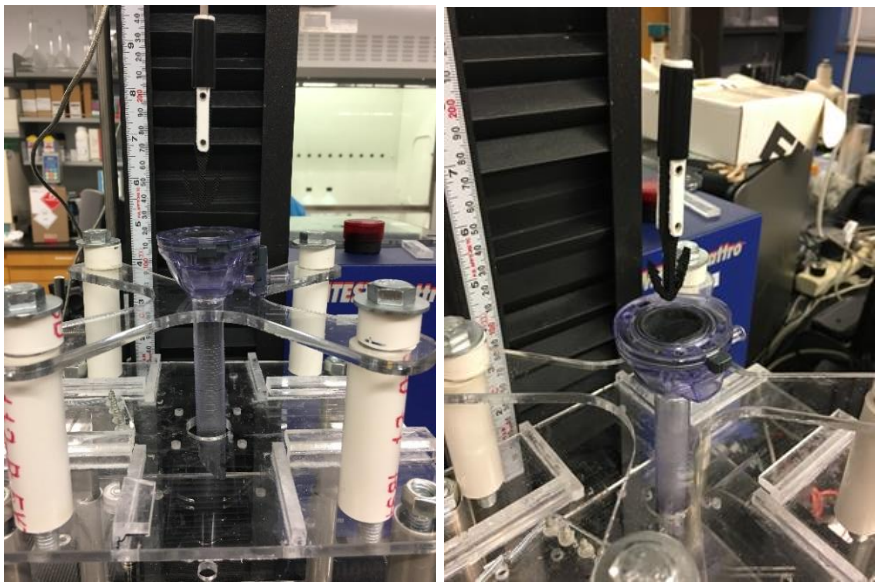


Figure 46: Test Set-up for PLA infill study.

3.3.4 Sharpening and Acetone Study

This study was conducted to mitigate proximal stem stress deformation upon insertion into a trocar and the problem of high delivery force required to penetrate tissue. Device sharpening was required for the penetration of the device into the fascia of the tissue. A blunt tip on the arms of the device increases the force required to penetrate tissue and increase the force on the arms of the device. Therefore, a fixture was created to sharpen the arm tips on the devices to improve tissue penetration and relieve the force on the device arms.

In addition, devices were treated in acetone to increase the flexibility of the device arms for easier insertion into the trocar. It is a known technique to rub acetone on PLA FDM printed part to soften the material. In this study, acetone was used to soften the device arms for increased flexibility.

The purpose of this study was to test the sharping fixture and the acetone treatment for effectiveness in device insertion and device penetration.

The tissue models used in this study will include the Dragon Skin silicone and Chicken thigh. Silicone materials have been used to simulate tissue biomechanics as related to deep tissue injury [12]. Chicken thigh was used because of its use in the design study: section 3.2.1.

This study included a three factor DOE with two factor levels, and 12 replicates. Using the data from the previous studies, power analysis estimated that 12 replicates would be needed to achieve a power greater than 90%. The responses recorded included insertion force and delivery force.

- Sharpening
    - Sharpened
    - Not Sharpened
- InFill Pattern
    - 95% Rectilinear (Acetone Treatment)
    - 95% Rectilinear (No Acetone Treatment)
- Tissue Model
    - Dragon Skin
    - Chicken

PLA with 95% infill was used in this study because of its positive results from the infill testing (referenced in section 4.2.1). Device manufacturing followed the same steps outlined in study 3.2.2 in terms of device PLA printing and laser cutting. Device were

then treated with a drop of acetone at the arms of the device as pictured in Figure 47 then left overnight to dry.

Figure 47: Drops of acetone on arms of the device to soften the PLA material.

Following laser cutting, devices were sharpened by the fixture depicted in Figure 36. Dimensions of the sharpening fixture can be found in Appendix section 6.3.

3.3.4.1 Application Fixture

The application device in Figure 48 was created for cadaver testing. The aluminum applicator has tapped hole at the proximal end that is compatible with a hand-held force gauge. The distal end of the device mimics the proximal shape of the device so that the device can be constrained. The distal holes were tapped to allow set screws to hold the TSCC in place. Dimensions of the applicator can be found in the Appendix section 6.4. Dragon skin silicone was cut to have an incision large enough to fit the trocar. The load frame mount to stabilize/orient the trocar was updated to be compatible in constraining both dragon skin and chicken thigh (Figure 51 and Figure 52).

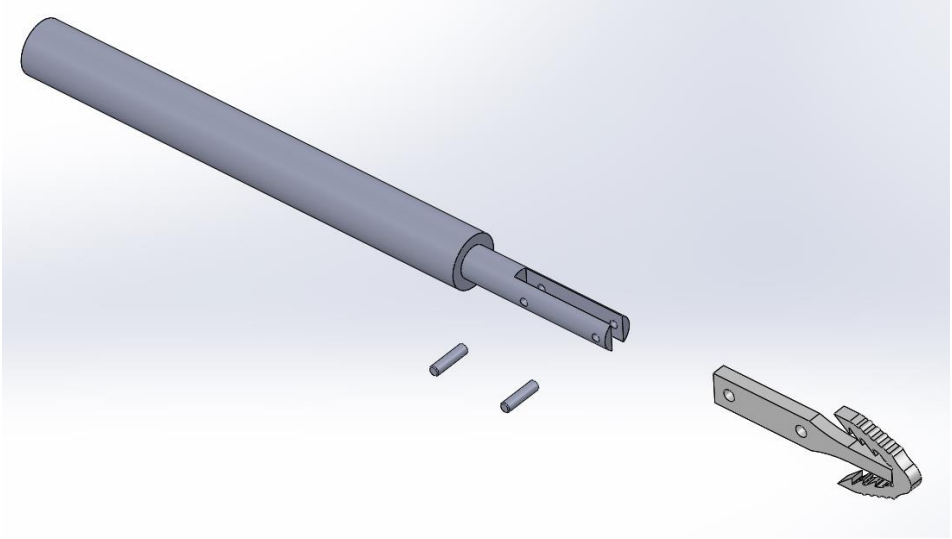


Figure 48: Expanded view of application device and TSCC assembly.

Figure 49: Application device in upright stance.

Figure 50: Small Incision made in Silicon for Trocar insertion.

Figure 51: Visual of test set-up before (top) and after (bottom) of trocar in and out of test fixture.

Load frame and device laser cutting were conducted as described in sections 3.3.1 and 3.2.2. The test fixture to constrain the tissue models followed the layout in study

3.3.1. However, for this study, clamps were added to the second tier to constrain the tissue models: chicken thigh and dragon skin silicon (Figure 52).

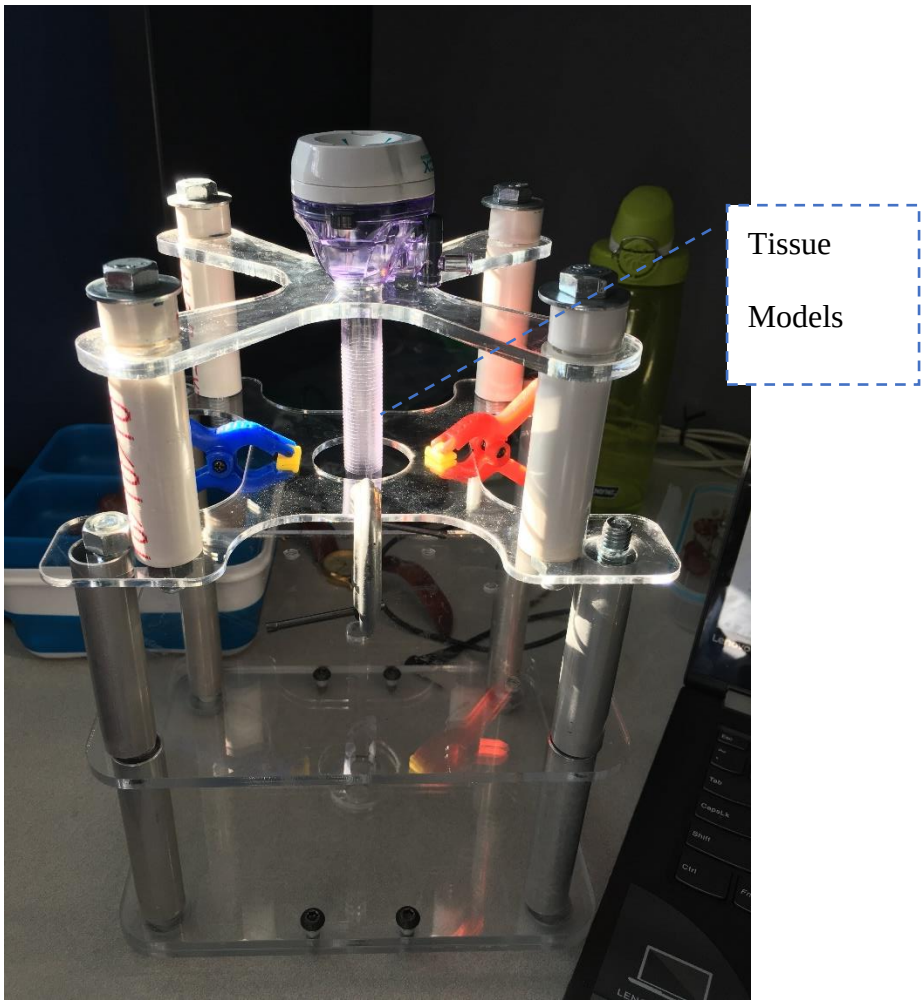


Figure 52: Devices sharpening and infill test fixture.

3.3.4.2 Dragon Skin Silicone Preparation:

The Dragon Skin Silicone was prepared to the specifications included in the package. The dragon skin silicone utilized is the *Smooth On: Dragon Skin Translucent Platinum Silicone* (Smooth On Inc., Macungie, PA). Figure 53 through Figure 56 show the process used to set the dragon skin silicone evenly and to the same depth. Plastic petri dishes were used for silicone setting. Each petri dished was filled to the same depth with

the wet dragon skin silicone to ensure consistency between batches. The silicone discs were cut into quarters for use in testing.

Figure 53: Separation of ingredients in two cups.

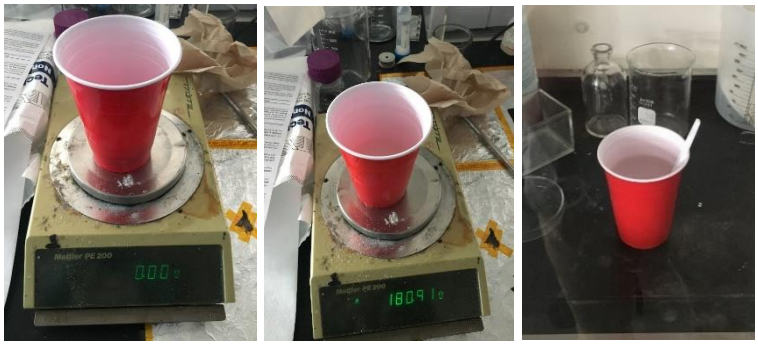


Figure 54: Weighing of mixture components (left and middle) and mixing of components in fume hood (right).

Figure 55: Measurement of petri dishes and pouring silicone into petri dishes.

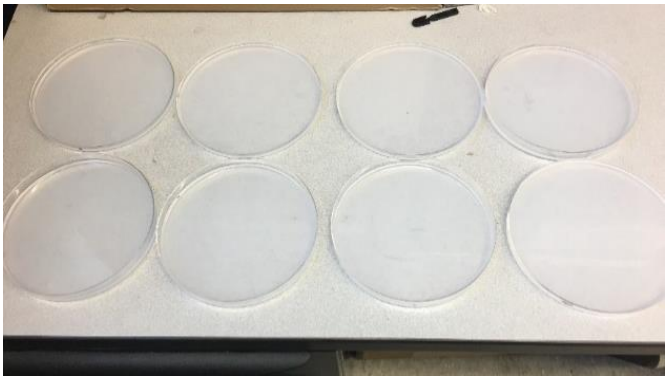


Figure 56: Allowing the silicone to dry in petri dish before cutting the specimen into quarters.

3.3.5 Revised Device Application Study

In evaluation of the devices during the cadaver testing, there was a necessary adjustment needing to be made to the design of the device. The applicator was updated to another model requiring a more rigid structure and holding the device at a more distal position. The new application device was planned to be used with an updated TSCC design. To hold the TSCC at a more distal point, the stem of the device was taken off. In addition, it was predicted that narrower arm stems would be needed to decrease the force required to deliver the TSCC into tissue. Lastly, to fit the new application device, Snowden-Pence lap tool, the TSCC were heated and stamped to merge the design of the Snowden-Pence applicator end effector to the proximal end of the TSCC. Figure 31 through Figure 34 depict the updated manufacturing steps to create the TSCC.

The methods of this study consisted of functional trials using the device prototype to plug trocar site sized incisions in dragon skin silicon and porcine belly. A full factorial design was created with two factors (material treatment and tissue model), two levels, with five replicates. The levels in this study included two different materials: PLA with acetone dip or PLA without acetone dip and two different tissue models: dragon skin silicone or porcine belly. Porcine belly squares prepared by a butcher was used in this

study as the second tissue model (Kingsley Meat and Catering, Louisville, KY). The porcine belly was positioned to be penetrated from the skin side to model, being a more rigid surface to penetrate. PLA devices were treated with acetone like the acetone treated devices in 3.3.4. The dragon skin silicone was prepared as described in section 3.3.4.2.

The responses test in this study were the insertion force (the peak force required to pass the device into the trocar, the delivery force (the peak force required to insert the device into the medium), and the retention force (the peak force withstood in attempts to dislodge the device out of the medium). The same load frame set-up was used from study 3.3.4 with the same sampling rate and load frame insertion/delivery rates. However, instead of using clamps to constrain the tissue model as performed in 3.3.4, a new Plexiglas® plate was used to constrain the tissue model. This change was made to simulate a more diffused surface force when holding the tissue models in place (shown in Figure 59). From this study the best prototype will be selected and utilized in another cadaver lab to prove efficacy of the design. Cadaver lab was conducted in the Fresh tissue lab at the University of Louisville Medical School with Dr. Daniel Metzinger.

Figure 57: Acetone treated devices drying.

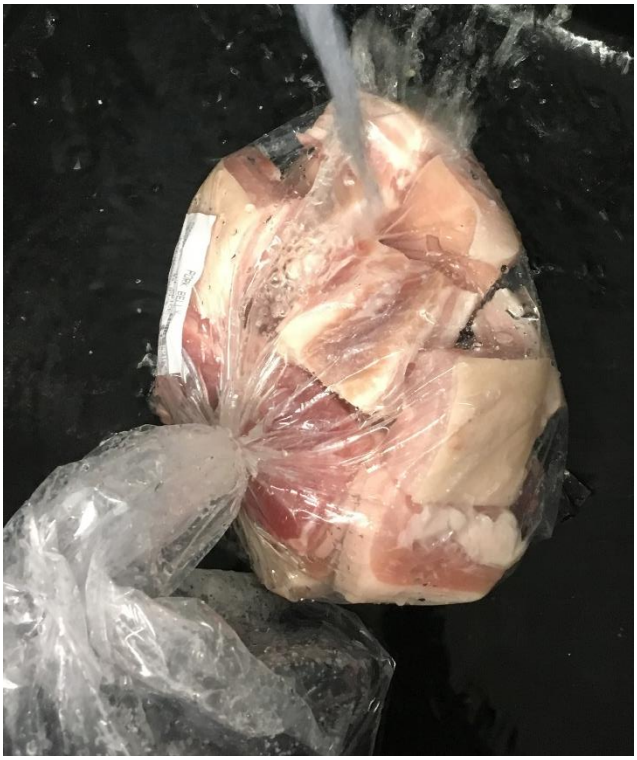


Figure 58: Preparation and thawing of frozen porcine belly squares.

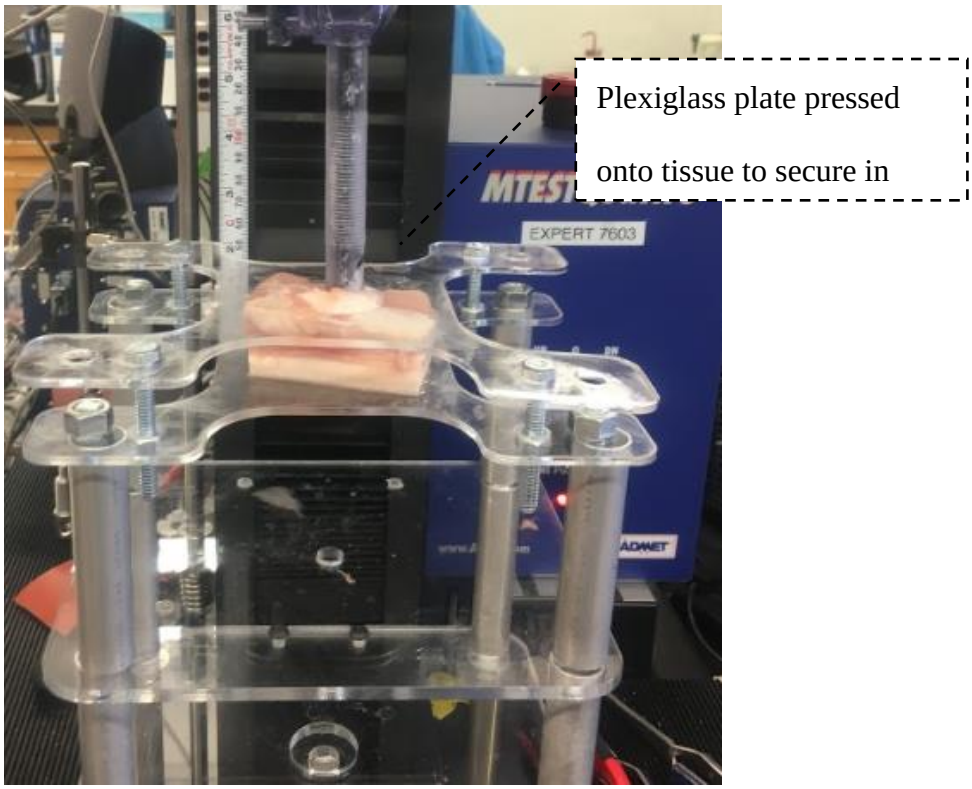


Figure 59: Delivery of updated TSCC devices into porcine belly squares.

3.4 Cadaver Studies

3.4.1 Cadaver 1 Study

The purpose of this study is to evaluate the ability of TSCC in sealing a 12mm trocar wounds in a cadaver. Cadaver tissue is to be an indicator of the effectiveness of the TSCC to penetrate living tissue. This study is an indicator of whether the TSCC is ready for further testing in chronic animal testing. Cadaver tissue is known to be less elastic than live tissue, so the cadaver tissue is meant to simulate a scenario that is harder to penetrate.

The cadaver was ordered through the University of Louisville Bioengineering department. The study was conducted at the University of Louisville School of Medicine in the fresh tissue lab. During this study the force to insert the TSCC and deliver the

TSCC was measured with a hand-held tensile force gauge and a custom application device shown in Figure 60.

Figure 60: The attachment of the applicator to the hand-held force gauge.

The updated and current design for the TSCC was compared to the past TSCC that were created in previous studies. The goal of the testing to demonstrate an improvement from the previous cadaver testing to show a decrease in force required to insert the TSCC into the trocar and the force required to deliver the TSCC into the tissue when compared to the previous design. Six of the previous devices were used in the study and six of the newly developed prototypes were tested in this study. The newly developed devices in this study were the 95% infill with acetone, sharpened devices tested in 3.3.4.

3.4.2 Cadaver 2 Study

The purpose of this study is to evaluate the ability of TSCC in sealing a 12mm trocar wounds in a cadaver. Cadaver tissue is to be an indicator of the effectiveness of the TSCC to penetrate living tissue. This study is an indicator of whether the TSCC is ready for further testing in chronic animal testing. Cadaver tissue is known to be less elastic than live tissue, so the cadaver tissue is meant to simulate a scenario that is harder to penetrate.

The cadaver was ordered through the University of Louisville bioengineering department. The study was conducted at the University of Louisville School of Medicine in the fresh tissue lab. During this study the force to insert the TSCC and deliver the TSCC was measured with a hand-held tensile force gauge and a custom application device.

This study was like the study conducted in 3.4.1 in terms of device preparation and the programing of the load frame. However, a new updated TSCC design was utilized as tested in 3.3.5. In this cadaver study a two factor DOE was conducted with two factor levels, and four replicates. The factors in this study was either a one barb design or a two-barb design, and if the TSCC devices were treated in acetone or not treated in acetone. Devices were inserted with the new application device as tested in 3.3.6. The hand-held force gauge was attached to the new applicator using the clamp in Figure 63.

Figure 61: Snowden-Pence Lap Tool Applicator.

Figure 62: Clamp placed onto Snowden-Pence Lap Tool.

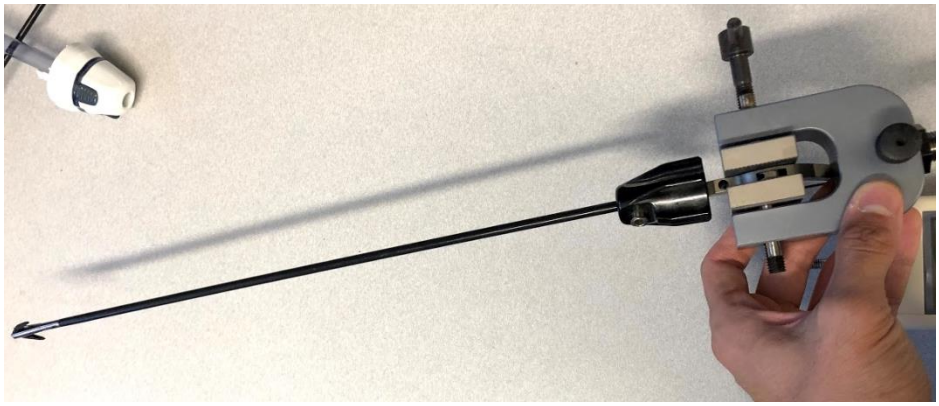


Figure 63: Attachment of clamp to hand-held force gauge depicting entire set-up for cadaver testing.

3.5 Short Chronic Animal Study

3.5.1 IACUC Proposal Methods

The purpose of this study is to evaluate the ability of TSCC in sealing a 12mm trocar wounds and to analyze the healing progression of tissue around the inserted device. For this study three 60kg pigs were ordered and tested under local anesthesia in the RRC at the University of Louisville hospital at different times. The IACUC test proposal can be found in the Appendix section 6.5 including the proposed test procedure, anesthesia protocol, and (pain management) protocol. The tested pigs were kept alive for seven days prior to euthanasian. Porcine tissue is to be an indicator of the effectiveness of the TSCC to penetrate living tissue and predictive of healing progression around the device in human tissue. This study is meant to provide proof of concept for the TSCC in effectively plugging, sealing trocar wounds, and preventing postoperative herniation. The animals were ordered through the University of Louisville bioengineering department. The study was conducted at the University of Louisville RRC along with help from trained IACUC veterinarians and technicians. During this study the force to insert the TSCC and deliver the TSCC was not measured with a hand-held tensile force gauge. The main objective of this study was to examine the healing progression of the TSCC device in a living model.

In this study, the sharpened, no acetone dip, one barb TSCC design was utilized as tested in 3.5.1. Due to the success of the one barb TSCC design in cadaver lab 2, and since retention force was not going to be measured, there was no need to test more than one TSCC design. A total of six trocar incisions were created in each pig and six devices were delivered in each pig. Devices were inserted with the new application device, Axillent Lap Tool (Karl Storz, Tuttlingen, Germany), tested in 3.4.2. The only difference

of this applicator is the distal grip design and proximal release mechanism. This change was to make testing easier for the surgeon. All the pigs were not tested on the same day and each pig did not receive TSCC from the same batch. A new batch of devices were created for each pig study. TSCC was sterilized prior to testing via ETO sterilization at the RRC. Before the chronic animal trials were conducted, test trials were prepared with a recycled rabbit carcass from another study. The rabbit was euthanized just before this trial run and a couple of TSCC devices were delivered into the tissue without any issues. Figure 64 through Figure 66 show images from this trial test setup.

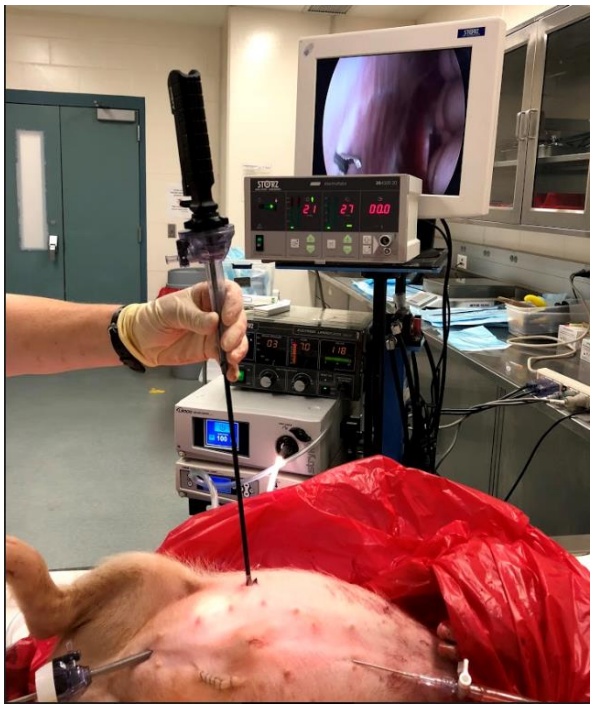


Figure 64: Trial of TSCC on Rabbit Carcass with Axillent Karl Storz Lap Tool Applicator.

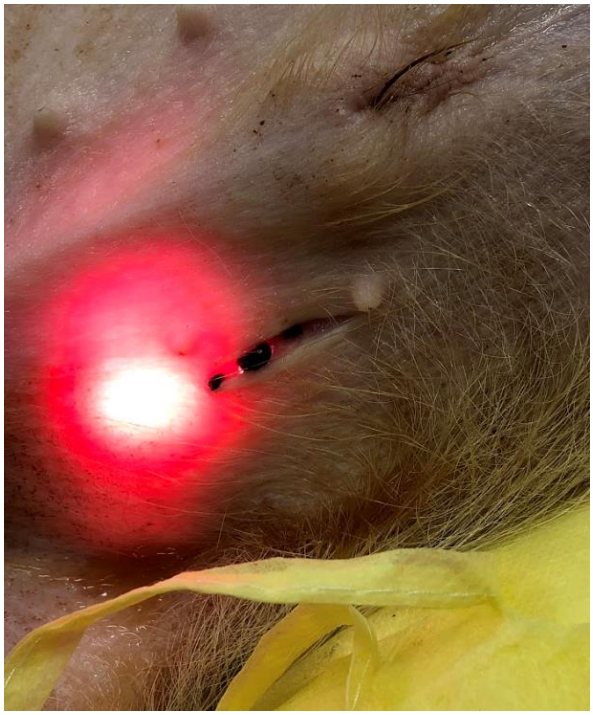


Figure 65: Picture of abdominal wall from the outside of carcass after device was inserted.

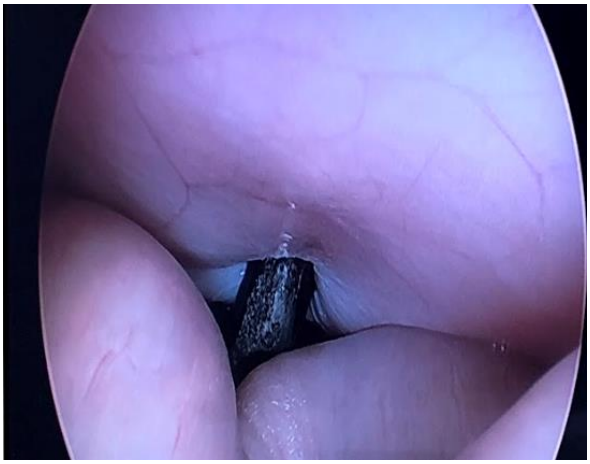


Figure 66: After closing the trocar wound with TSCC device in trial carcass.

3.5.2 Histology Preparation

Seven days after the procedure, the animals were euthanized, and the trocar sites were harvested and set in formaldehyde. The harvested devices were shipped to Mass Histology in Worcester, MA for histology of the trocar sites. All sites, whether they were successfully plugged, or open wounds were sent for histology. The services requested

include slide preparation from tissue equally spaced from the axis of the trocar wound, trichrome staining, a semi-qualitative report analyzing for newly formed collagen fibers, and annotated photography showing new collagen formation of tissue near implanted device in container. The goal of the histology was to help analyze/compare the presence of new collagen fibers near the incision site, the implanted device, around the healing wound, and to get an impression of the device biocompatibility in an animal.

A 2017 publication studying *The Biodegradation and Biocompatibility of Poly L-lactic Acid (PLLA) implantable Mesh* performed an in vitro and in vivo 180-day evaluation of alterations in weight, tensile strength, inflammatory response. The study found that "the weight and tensile strength of the PLLA prosthesis was stable for 180 days. In addition, the surface of the PLLA mesh was not digested under in vitro or in vivo conditions as determined by scanning electron microscope. Histologically, there were no significant changes in the diameters of implanted PLLA mesh and subtype fibers over the course of 180 days. Likewise, there were no significant changes in the number of inflammatory and mast cells after 180 days, nor was there an increase in the percentage of collagen surrounding the PLLA mesh" [13]. Results indicated that PLLA mesh did not induce inflammation in subcutaneous tissue; however, according to other literature, may induce inflammation in different tissues or under specific incubation conditions. The goal is for this study's histological findings to determine the biocompatibility of PLA (from this study) in peritoneal tissue.

IV. RESULTS AND DISSCUSSION

4.1 Design Results

4.1.1 Device Distal Stem Design Results

This study was conducted to determine the distal end effector design that is most effective for parameters laid out for the TSCC in Section 3.1. The goal was to find the distal design that requires the lowest insertion force and the design that can withstand the highest delivery force. The results of this study show that there were significant differences between the designs and thicknesses during the insertion of the devices into the 12mm trocar, but no significant difference caused by the interactions of the factors, as seen in Figure 67**.** The main effects were plotted for insertion forces of the devices and designs 1, 2, 3, 4, 5 had an average insertion force of 2.06lbs, 2.84lbs, 1.65lbs, 1.79lbs, and 2.29lbs respectively. The Tukey pairwise comparisons are shown in Figure 69. From the Tukey pairwise comparison it can be determined that designs 2 and 5 had a significantly higher insertion force and designs 1, 4, 3, had a significantly lower insertion force also shown by the main effects plot in Figure 68. Thickness of 1/16” had an average insertion force of 1.66lbs, and thickness of 1/8” had an insertion force of 2.600lbs.

General Linear Model: Insertion Force versus Design, Thickness, Tube Delivery

Method

Factor coding (-1, 0, +1)

Factor Information

Factor	Type	Levels	Values
Design	Fixed	5	1, 2, 3, 4, 5
Thickness	Fixed	2	0.06, 0.13
Tube Delivery	Fixed	2	1, 2

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Design	4	10.4795	2.6199	9.37	0.000
Thickness	1	13.2893	13.2893	47.52	0.000
Tube Delivery	1	0.2150	0.2150	0.77	0.386
Design*Thickness	4	1.1976	0.2994	1.07	0.384
Design*Tube Delivery	4	1.4633	0.3658	1.31	0.283
Thickness*Tube Delivery	1	0.6878	0.6878	2.46	0.125
Design*Thickness*Tube Delivery	4	0.9859	0.2465	0.88	0.484
Error	40	11.1857	0.2796		
Total	59	39.5041			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.528813	71.68%	58.23%	36.29%

Figure 67: Analysis of Variance in Insertion Force.

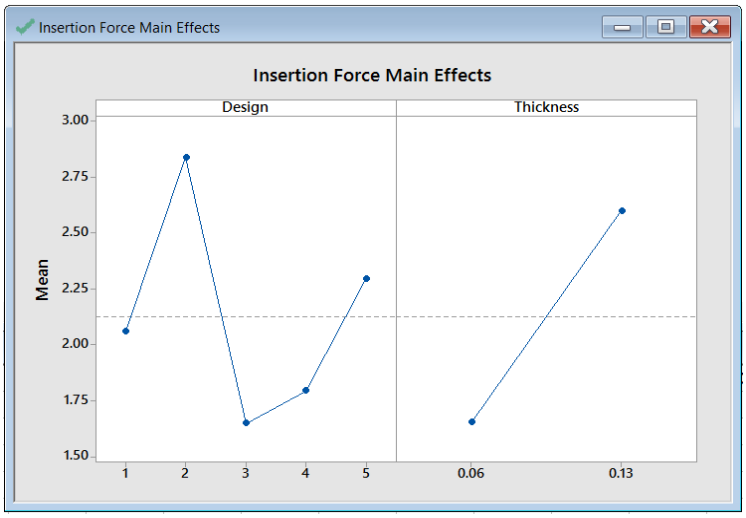


Figure 68: Main Effects Plot of Insertion Force.

Comparisons for Insertion Force

Tukey Pairwise Comparisons: Response = Insertion Force, Term = Design

Grouping Information Using the Tukey Method and 95% Confidence

Design	N	Mean	Grouping		
2	12	2.83657	A		
5	12	2.29356	A	B	
1	12	2.06089		B	C
4	12	1.79395		B	C
3	12	1.65079			C

Means that do not share a letter are significantly different.

Tukey Pairwise Comparisons: Response = Insertion Force, Term = Thickness

Grouping Information Using the Tukey Method and 95% Confidence

Thickness	N	Mean	Grouping	
0.13	30	2.59770	A	
0.06	30	1.65653		B

Means that do not share a letter are significantly different.

Figure 69: Tukey Pairwise Comparison of Insertion Force.

In addition, the results of this study show that there were significant differences in delivery force caused by the thickness of the designs and by the interactions between the design, thickness, and tube delivery system as seen in Figure 70. The delivery force interaction plot in Figure 71 shows that devices with a thickness of 1/8” can withstand a significantly higher delivery force. The delivery forces for designs 1, 2, 3, 4, 5 at thickness of 1/8” and tube delivery 1 had an average of 17.24lbs, 15.94lbs, 34.70lbs, 29.30lbs, 18.32lbs respectively. The Tukey pairwise comparisons are shown in Figure 72. From that chart it can be determined which group of devices had the highest delivery forces under which interactions. It is also shown that for designs 4, 1, and 5, the tube delivery method did not have a significant effect on delivery force. High delivery force means that the design can withstand more force and is a more superior design compared to the others. This can be emphasized by the fact that the design changes are only applicable to the end effectors and not the device arms.

General Linear Model: Delivery Force versus Design, Thickness, Tube Delivery

Method

Factor coding (-1, 0, +1)

Factor Information

Factor	Type	Levels	Values
Design	Fixed	5	1, 2, 3, 4, 5
Thickness	Fixed	2	0.06, 0.13
Tube Delivery	Fixed	2	1, 2

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Design	4	181.85	45.46	1.93	0.125
Thickness	1	1587.62	1587.62	67.26	0.000
Tube Delivery	1	0.32	0.32	0.01	0.908
Design*Thickness	4	219.44	54.86	2.32	0.073
Design*Tube Delivery	4	291.55	72.89	3.09	0.026
Thickness*Tube Delivery	1	119.18	119.18	5.05	0.030
Design*Thickness*Tube Delivery	4	645.44	161.36	6.84	0.000
Error	40	944.16	23.60		
Total	59	3989.56			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
4.85839	76.33%	65.09%	46.75%

Figure 70: Analysis of Variance of Delivery Force.

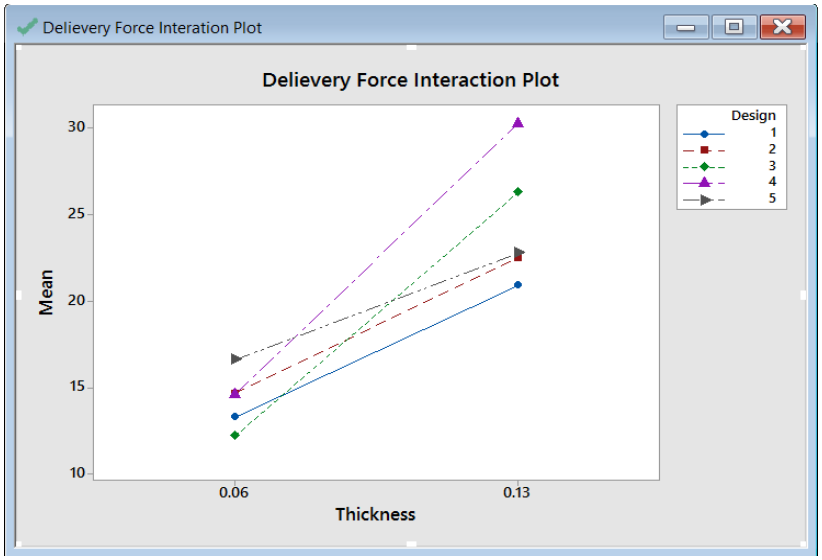


Figure 71: Interaction Plot of Delivery Force.

Tukey Pairwise Comparisons: Response = Delivery Force, Term = Design*Thickness*Tube Delivery

Grouping Information Using the Tukey Method and 95% Confidence

Design*Thickness*Tube

Delivery	N	Mean	Grouping					
3 0.13 1	3	34.7011	A					
4 0.13 2	3	31.2397	A	B				
4 0.13 1	3	29.3047	A	B	C			
2 0.13 2	3	29.1657	A	B	C			
5 0.13 2	3	27.3094	A	B	C	D		
1 0.13 2	3	24.6634	A	B	C	D	E	
5 0.13 1	3	18.3165		B	C	D	E	F
1 0.06 1	3	18.0199		B	C	D	E	F
3 0.13 2	3	17.9379		B	C	D	E	F
1 0.13 1	3	17.2353		B	C	D	E	F
5 0.06 1	3	16.9105		B	C	D	E	F
2 0.06 1	3	16.5838		B	C	D	E	F
5 0.06 2	3	16.3661		B	C	D	E	F
2 0.13 1	3	15.9356			C	D	E	F
4 0.06 1	3	15.3034			C	D	E	F
4 0.06 2	3	13.9314				D	E	F
3 0.06 2	3	13.1039				D	E	F
2 0.06 2	3	12.7791				D	E	F
3 0.06 1	3	11.3296					E	F
1 0.06 2	3	8.6023						F

Means that do not share a letter are significantly different.

Tukey Pairwise Comparisons: Response = Delivery Force, Term = Thickness*Tube Delivery

Grouping Information Using the Tukey Method and 95% Confidence

Thickness*Tube

Delivery	N	Mean	Grouping	
0.13 2	15	26.0632	A	
0.13 1	15	23.0986	A	
0.06 1	15	15.6295		B
0.06 2	15	12.9565		B

Means that do not share a letter are significantly different.

Figure 72: Tukey Pairwise Comparison of Delivery Force.

To distinguish the most effective design for the purposes of this application, a decision matrix was created as seen in Table 2. This decision matrix was used to rank the TSCC designs by their insertion force averages, delivery force averages, and the ease of testing. The delivery force averages were weighted higher than the insertion force, and the insertion force averages were weighted higher than the ease of testing. Each category of the decision matrix was given a number to rank its performance in testing. The higher the number, the more desired the result. In this case, lower insertion forces were desired and higher delivery forces were desired. The tube delivery 2 was more preferred than tube delivery 1 because of the less time required in testing. The distal design of device 4

led to showing that the design was capable to withstand the highest delivery force while minimizing the force required to insert the device into the trocar. The other distal designs did not show this trend to the extent that design for did. After totaling the results, design 4 at 1/8" was selected to be used in further studies.

Table 2: Decision Matrix for Optimal End Effector TSCC Design.

Prototype Factors	Delivery Force- 3	Insertion Force- 2	Ease of Testing- 1	
Design 3, 1/8", 1	High- 3x3= 15	Medium- 2x2= 4	Low- 1x0= 0	19
Design 3, 1/16", 1	Low- 3x1= 3	Low- 2x3= 6	Low- 1x0= 0	9
Design 3, 1/8", 2	Medium- 3x2= 6	Medium- 2x2= 4	High- 1x1= 1	10
Design 3, 1/16", 2	Low 3x1= 3	Low- 2x3=6	High- 1x1= 1	9
Design 4, 1/8", 1	High- 3x3= 15	Medium- 2x2= 4	Low- 1x0= 0	19
Design 4, 1/16", 1	Low- 3x1= 3	Low- 2x3= 6	Low- 1x0= 0	9
Design 4, 1/8", 2	**High- 3x3= 15**	**Medium- 2x2= 4**	**High- 1x1= 1**	**20**
Design 4, 1/16", 2	Low- 3x1= 3	Low- 2x3= 6	High- 1x1= 1	10

4.1.2 Dakota Prototype Material Study

Summaries for the results of the two devices tested can be found in Figure 73 and Figure 74. For the results of this study a non-normal, Kruskal Wallis test (Figure 75) performed after unsuccessful attempts to transform the non-normal data from both materials. The transformation used include: sqrt(t); 1/sqrt(1); ln(y); log10(y). In comparison of the two PLA materials, the ECOMAX PLA and the PLA material used by the previous student differed in their peak tensile forces. The average peak break force of the Advanced Solution devices was 24.9lbs (Figure 73) and the average peak break force of the ECOMAX devices was 20.62lbs (Figure 74). Even though the testing shows that

there is a significant difference in the peak forces of these two PLA materials, the ECOMAX devices are still an applicable choice. The ECOMAX devices having a maximum peak load of 20.62lbs should be more than enough for the requirement of our devices. For clinical circumstances, the devices should need no more than 10lbs force for the device to be delivered into tissue. Since the ECOMAX devices had a peak force of two times what should be necessary, it can be considered a viable candidate for prototyping.

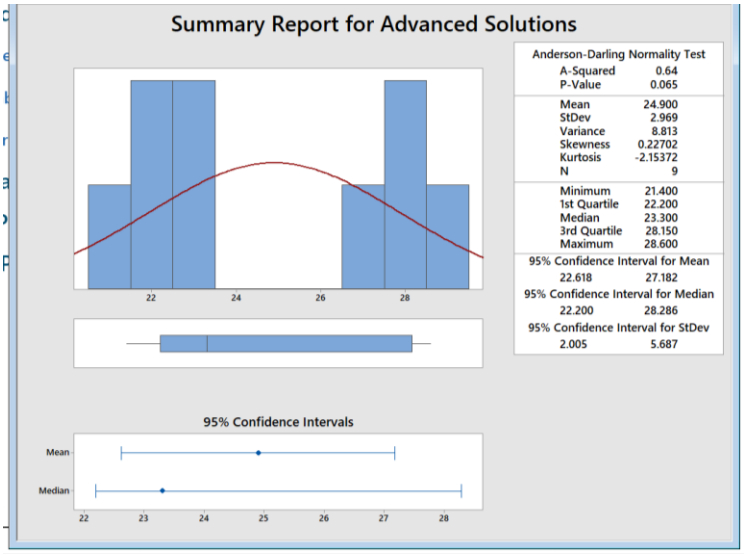


Figure 73: Summary of Advanced Solutions Devices.

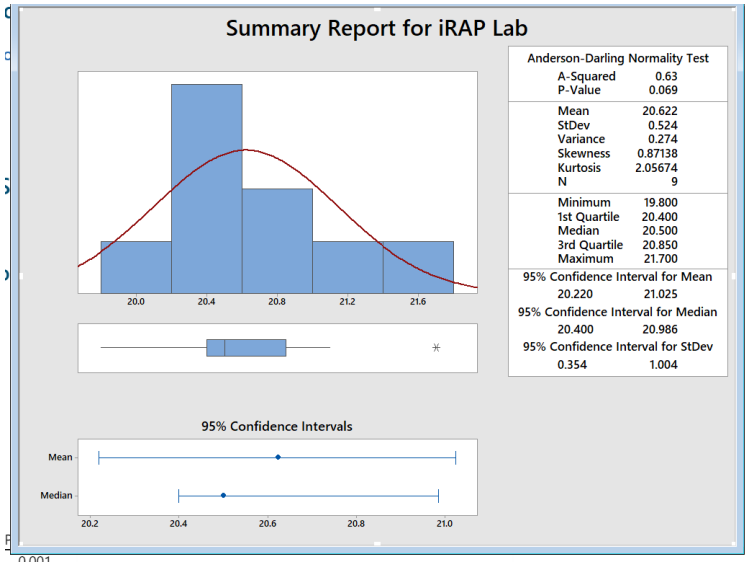


Figure 74: Summary of ECOMAX devices.

Kruskal-Wallis Test: Peak Force versus Material

Descriptive Statistics

Material	N	Median	Mean Rank	Z-Value
1	9	23.3	13.9	3.49
2	9	20.5	5.1	-3.49
Overall	18		9.5	

Test

Null hypothesis H_0: All medians are equal
Alternative hypothesis H_1: At least one median is different

Method	DF	H-Value	P-Value
Not adjusted for ties	1	12.17	0.000
Adjusted for ties	1	12.23	0.000

Figure 75: Kruskal-Wallis Test for Material Study.

4.2 Benchtop Studies Results

4.2.1 Infill Study

The goal of this study was to optimize the infill percentage of the devices to have the most effective insertion forces while not compromising the delivery force tensile strength. The 70%, 80%, and 90% devices broke upon insertion into the trocar. The

devices were too fragile to make it into the trocar without fracturing inside. Figure 76 shows the failure of a device after insertion into a trocar.

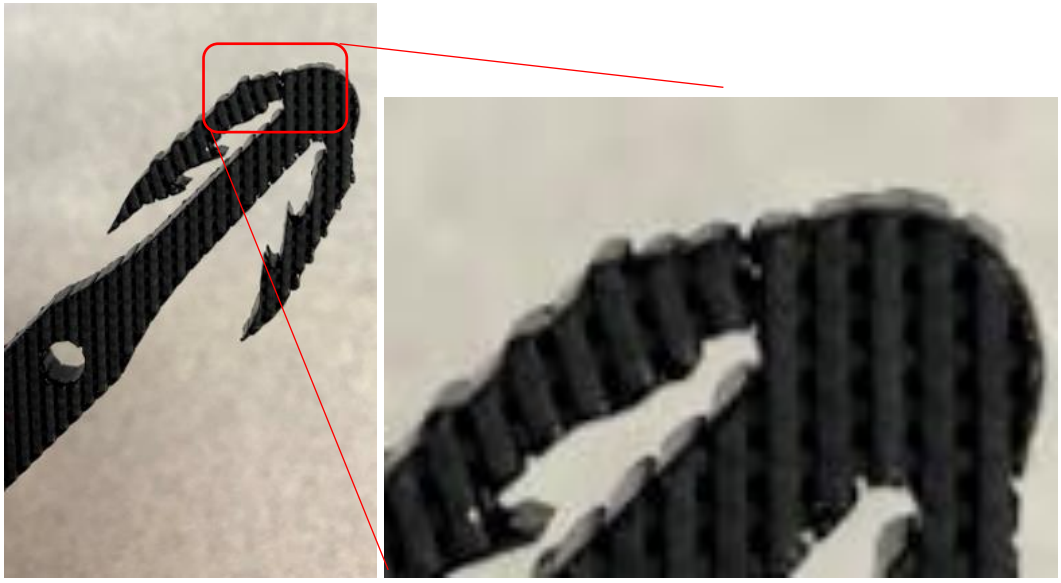


Figure 76: Fracture of the left? device arm.

The 100% infill devices were the only devices that made it through the trocar intact, however, the devices had stress notches on the distal end. The devices were compromised by the stress notches and the delivery device force varied between runs. Figure 78 and Figure 79 shows end of the delivery force test and the breakage of the other infill devices. Due to the variability of the 100% devices and the failure of the 70%, 80%, 90% devices failed during insertion, a linear regression couldn't be made. Therefore, a fifth infill percentage was created and tested at 95% infill. Figure 77 shows the results for testing with the 95% infill. Tensile forces for 70%, 80%, and 90% are the tensile break forces. The 95% infill devices didn't always show signs of stress notches forming on the distal end due to the compression of the device arms when passing through the trocar. The delivery force of the 95% devices were more consistent and showed less sign of device stress.

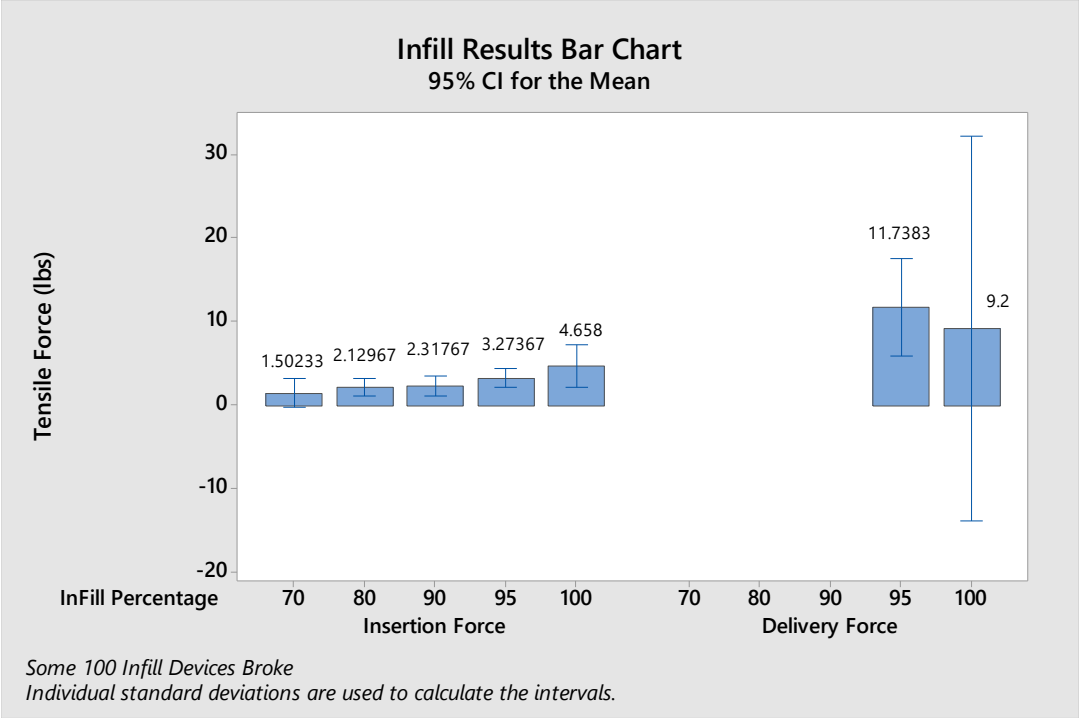


Figure 77: Bar Plot of Insertion Force and Delivery Force in PLA Infill Study.

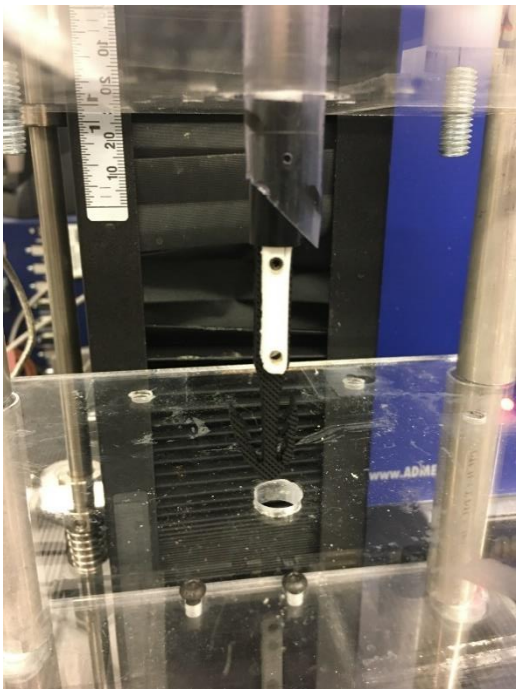


Figure 78: Device failure of 80% Infill Device Upon Insertion into Trocar.

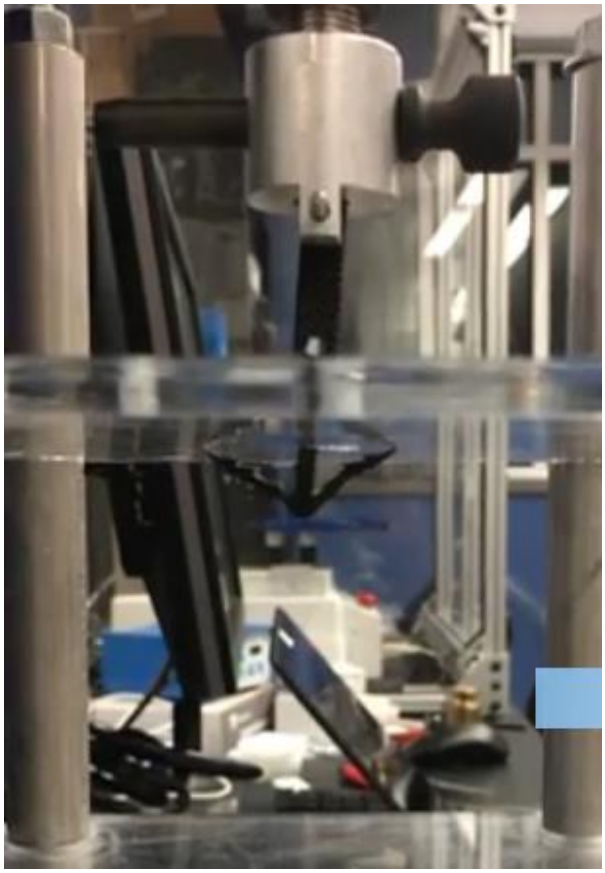


Figure 79: Device Tensile Force Break Point Testing.

4.2.2 Sharpening and Acetone Study

The results of the benchtop study comparing acetone treatment to non-acetone treatment along with a comparison of tissue models are shown as a Bar plot in Figure 80.

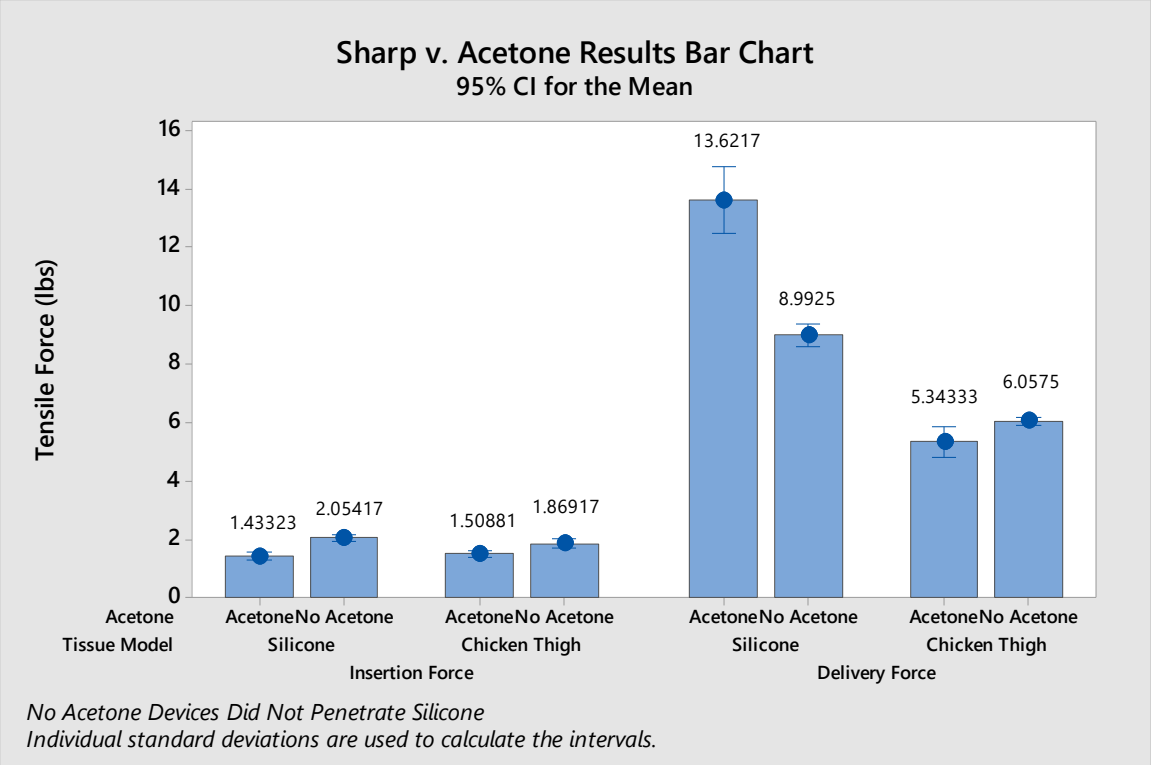


Figure 80: Bar Plot from Benchtop Testing of Acetone/Non-Acetone treated devices in both tissue models.

In the bar plot in Figure 80, the Acetone 1 refers to devices that did have the acetone treatment, and Acetone 2 refers to devices that did not have the acetone treatment. Tissue model 1 refers to delivery of the devices into the dragon silicone, and Tissue model 2 refers to delivery of the devices into the chicken thigh. The devices that were not treated with acetone plastically deformed during insertion into the trocar and were compromised before being delivered into the tissue model. Due to this, the non-acetone treated devices never pierced the silicone and the arms snapped off. The acetone treated devices had a lower insertion force than the non-acetone devices. During insertion, the acetone treated devices were able to flex and did not fracture during insertion into the trocar. The allowed the acetone treated devices to remain intact and maintain the structural integrity pierce through the silicone. Both the non-treated and treated devices were able to pierce the chicken thigh. Due to these results, the acetone

treated devices were selected to be used in the cadaver lab. Averages for the benchtop testing are labeled in Figure 80. Pictures from testing are shown in Figure 81 through Figure 84.

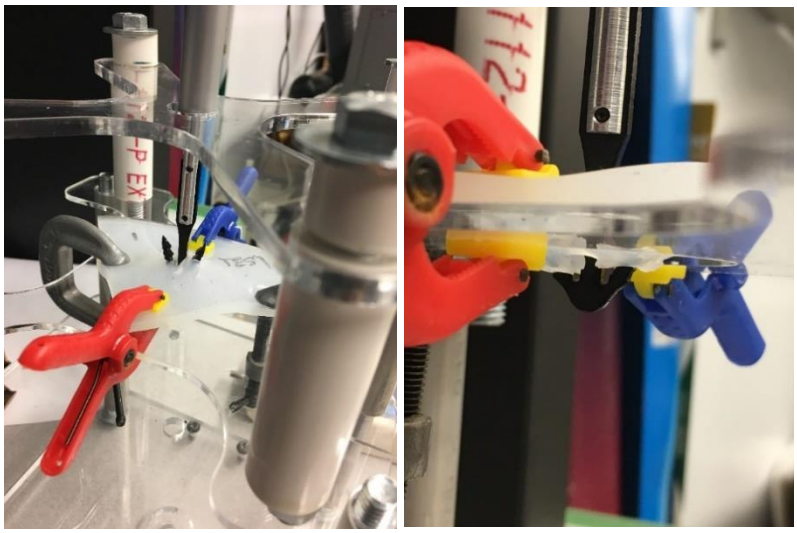


Figure 81: Acetone treated devices piercing the dragon skin silicone during testing.

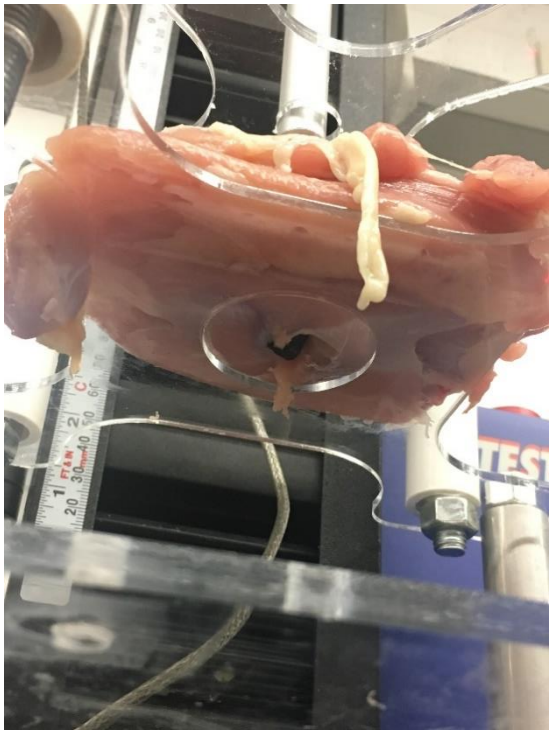


Figure 82: Underneath view of the TSCC successfully penetrating chicken thigh.

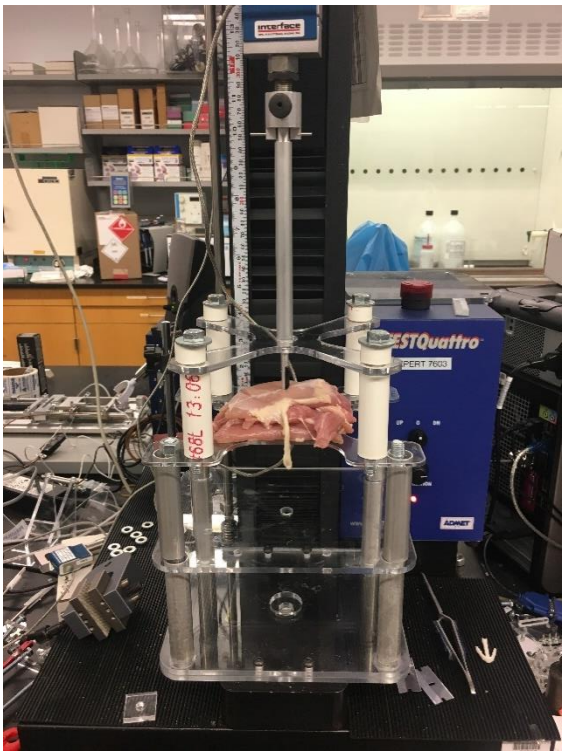


Figure 83: Front view of the bench top testing.


Figure 84: Devices laid out prior to testing.

4.2.3 Revised Device Application Study

In this study, both acetone-treated and non-acetone treated, were evaluated in dragon skin silicone and porcine belly, respectively. The non-acetone treated PLA

devices required an average of 2.7lbs insertion force to pass into the trocar, and a 6.46lbs delivery force to pierce into dragon skin and an 8.67lbs delivery force to pierce into the porcine belly (Figure 86 and Figure 87). The acetone treated PLA devices failed during the delivery process into both the dragon skin and porcine belly tissue models with an average failure force of 5.76lbs and 9.7lbs, respectively. Therefore, only the non-acetone treated PLA devices were used in the cadaver lab to prove the efficacy of the devices. Figure 87 and Figure 88 show the failure of an acetone device failing in dragon skin silicone and a successful non-acetone device penetrating porcine belly, respectively. The acetone dip for these devices made the material too fragile to penetrate the tissue models effectively. The narrowed device design for these prototypes proved to be effective in naturally allowing the device arms to flex through the trocar without acetone treatment.

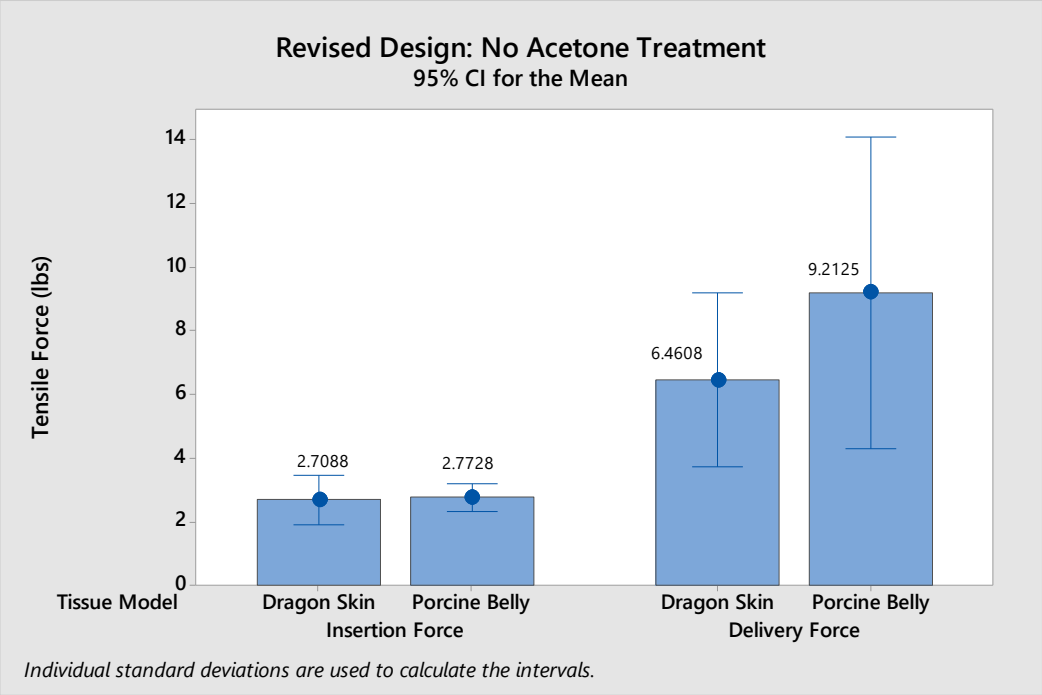


Figure 85: No Acetone Treatment Devices Plot of Insertion Force and Delivery Force.

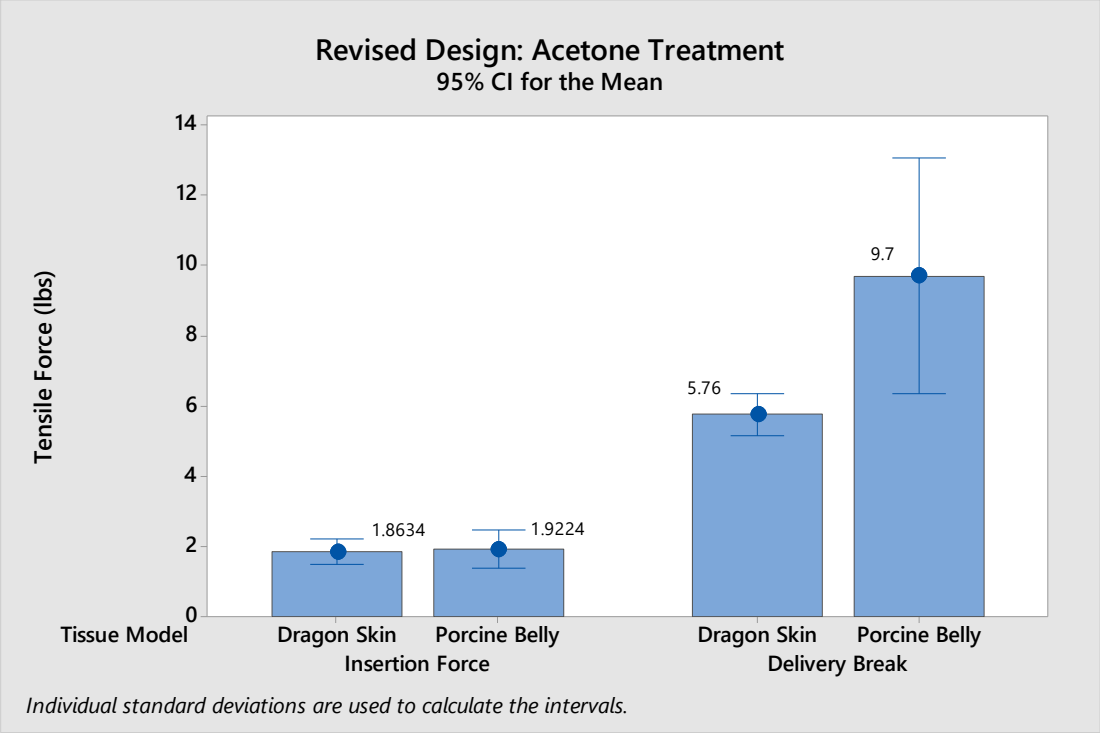


Figure 86: Acetone Devices Plot of Insertion Force and Delivery Force.

Figure 87: Broken Acetone treated device during delivery into dragon skin silicone.

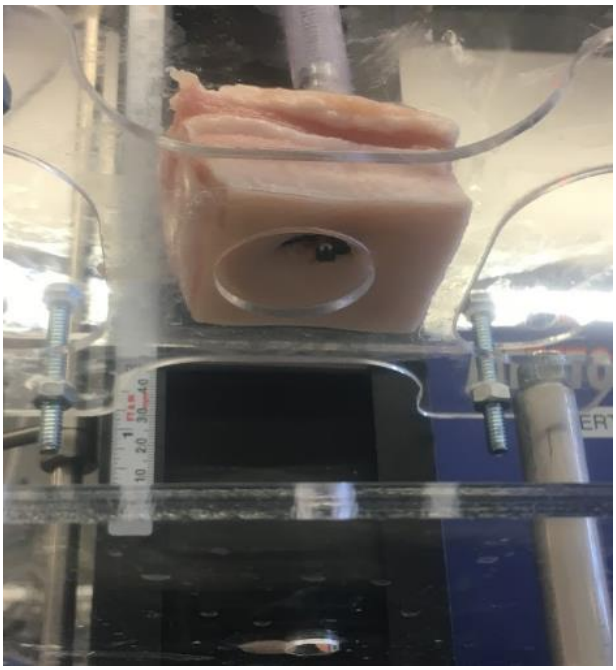


Figure 88: Successful delivery of non-acetone treated device into porcine belly.

4.3 Cadaver Studies Results

4.3.1 Cadaver 1 Study

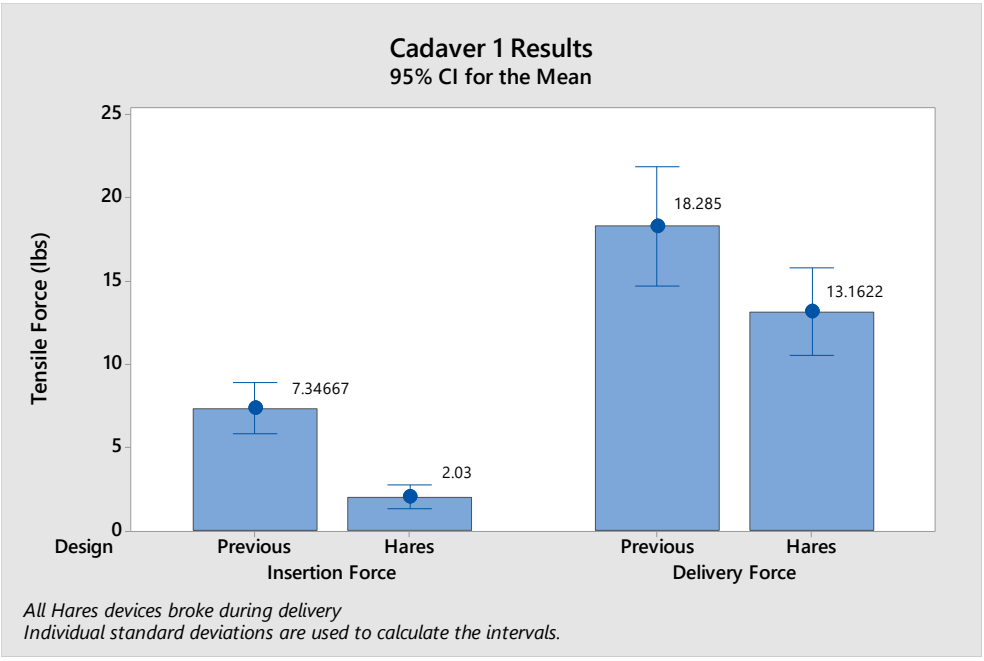


Figure 89: Bar Plot of Insertion Force and Delivery Force for "Previous" and "Hares" Devices.

The devices labeled “Hares” in this study corresponded to the device that were made with the most updated device design described in the methods of this study. The devices labeled “Previous” correspond to the devices that were made by the previous student. The “Hares” devices broke upon delivery into the cadaver tissue at an average tensile force of 13.16lbs. The “Previous” devices had stress notches when passing through the trocar and required an average of 7.34lbs. The “Previous” devices delivered into the cadaver tissue required an average of 18.29lbs force to penetrate the tissue. The insertion force for the “Hares” devices was an average of 5.31lbs lower to pass through the trocar. The insertion force of the “Full devices was described as an acceptable amount of force to apply when pushing a device into the trocar, per the surgeon. The surgeon also mentioned that having a delivery force of 18.29lbs was too great for surgeons to perform in live laparoscopic procedures. Figure 90 and Figure 91 show the delivery and insertion of the “Previous” devices in the abdominal cavity.

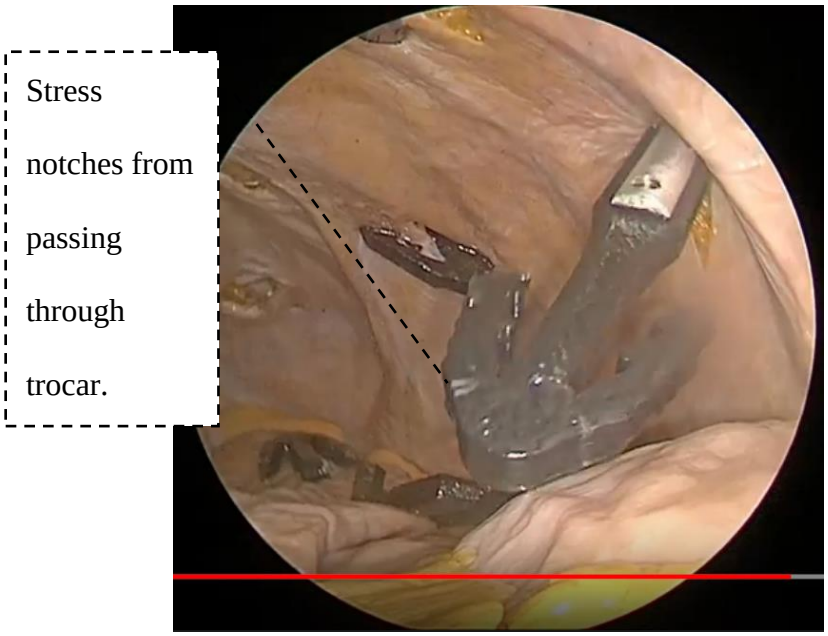


Figure 90: Picture of the "Previous" Device in cadaver abdominal cavity before delivery.

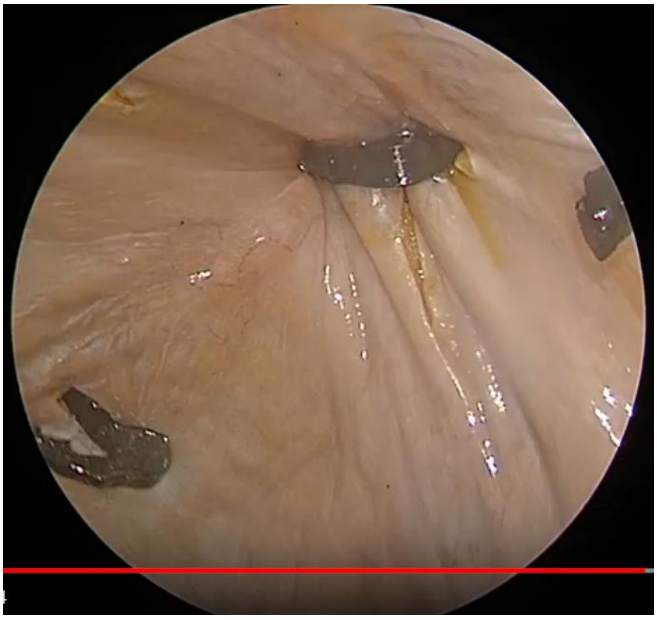


Figure 91: Delivery of the "Previous" device into cadaver tissue to plug trocar site.

After the “Hares” devices showed a consistent pattern of failure a new method was attempted in delivering the TSCC device. Instead of pulling the device from the proximal stem, a TSCC device was broken at the stem and a laparoscopic tool was used to grip the device from the distal end as shown in Figure 92. The prototype device was successful upon delivery into the cadaver tissue (Figure 93).

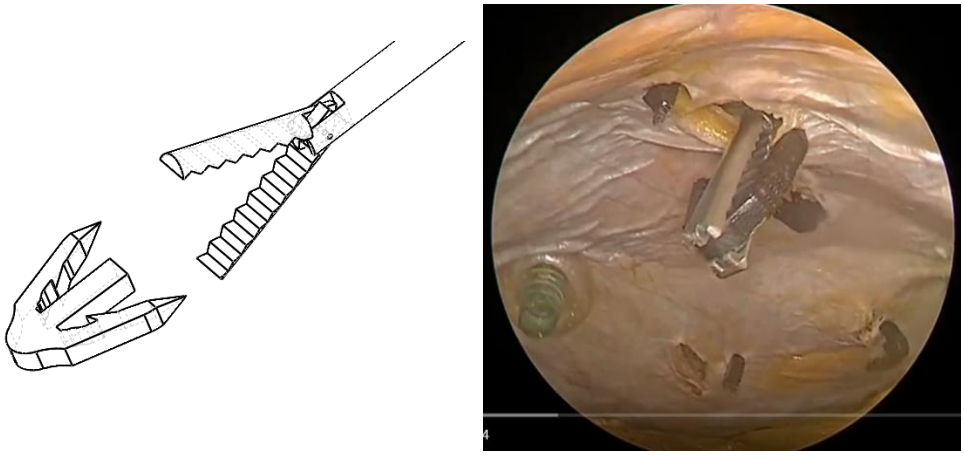


Figure 92: Hares devices (without stem) in cadaver abdominal cavity before delivery.

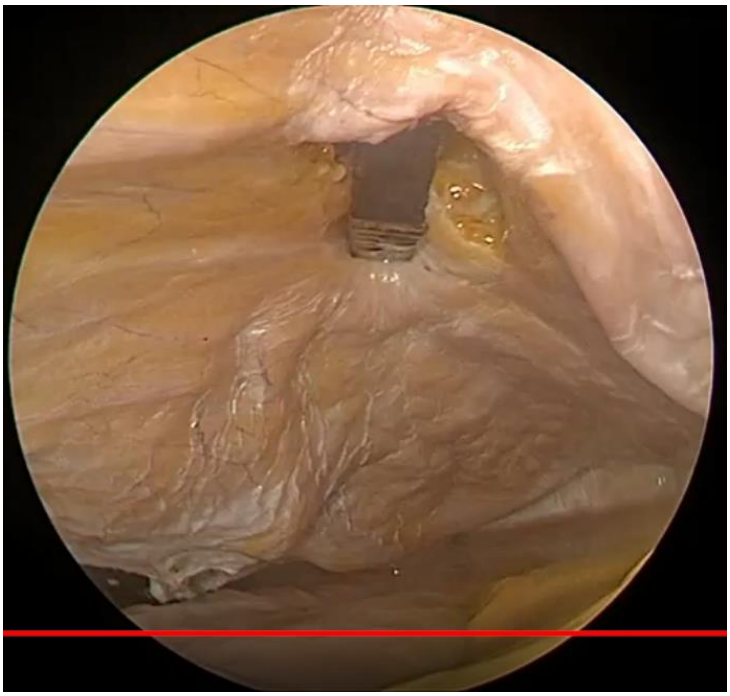


Figure 93: Successful plug of trocar site with "Hares" devices without device stem.

4.3.2 Cadaver 2 Study

Ten devices were inserted into the abdominal cavity of a cadaver through a 12mm car and delivered into the peritoneum and fascia. The trocar wound was successfully plugged and sealed for potential hernia prevention (Figure 95 and Figure 96). Five of each group were measured for insertion force and delivery force, and two from each group were measured for retention force in the cadaver tissue. The average values measured were 2.57lbs, 11.78lbs, 6.98 lbs, respectively (Figure 94). These devices differed in their barb design. The one barb devices were more effective in delivering into tissue because of the less resistance occurring on one barb device when compared to two barb devices. The second barb on the two barb devices proved to be too much resistance in some cases and led to device failure for 3/5 devices inserted. The bar chart shows the tensile break point in this case. The great variability found in the measurement of the

retention force is likely due to the difficulty in measuring retention force in live tissue. Pushing the devices out was hard to capture when the devices needed to be pushed into the intestines of the animal.

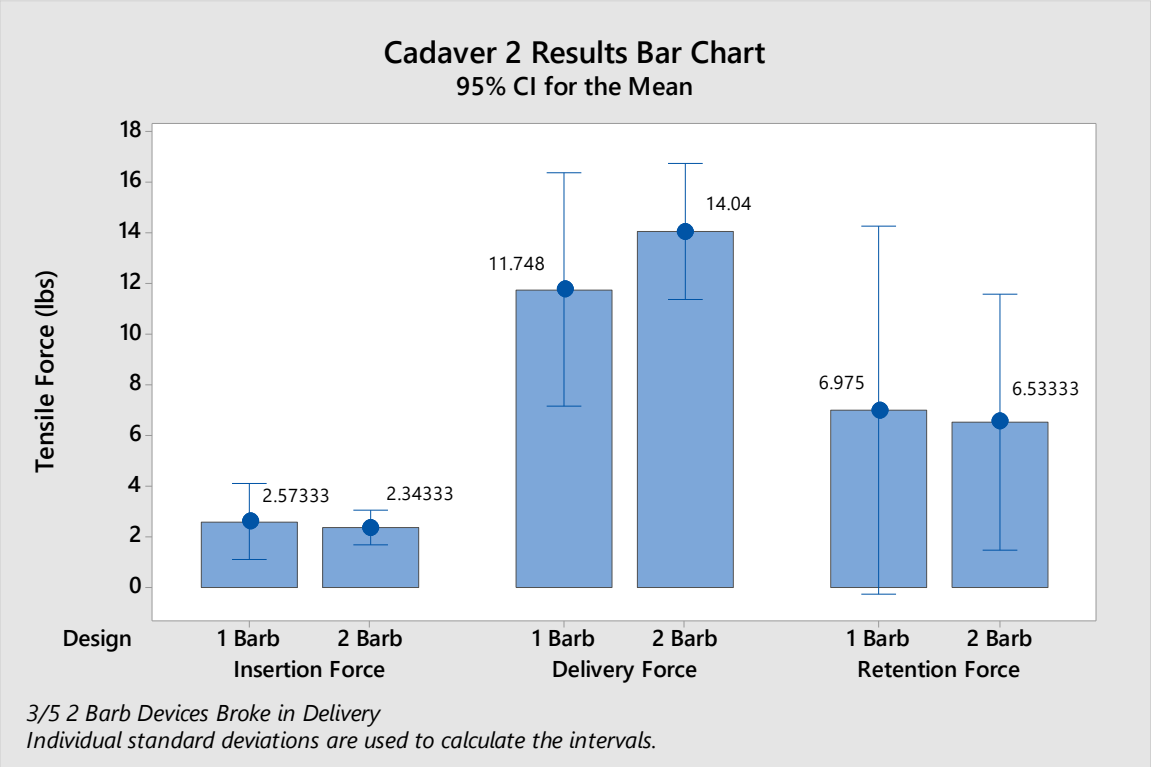


Figure 94: Bar Plot of Insertion, Delivery, and Retention Force in Cadaver Lab.

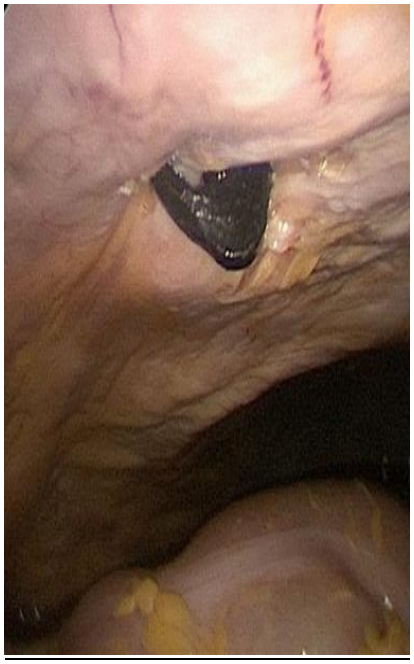


Figure 95: Successful Device Delivery into Cadaver Tissue.

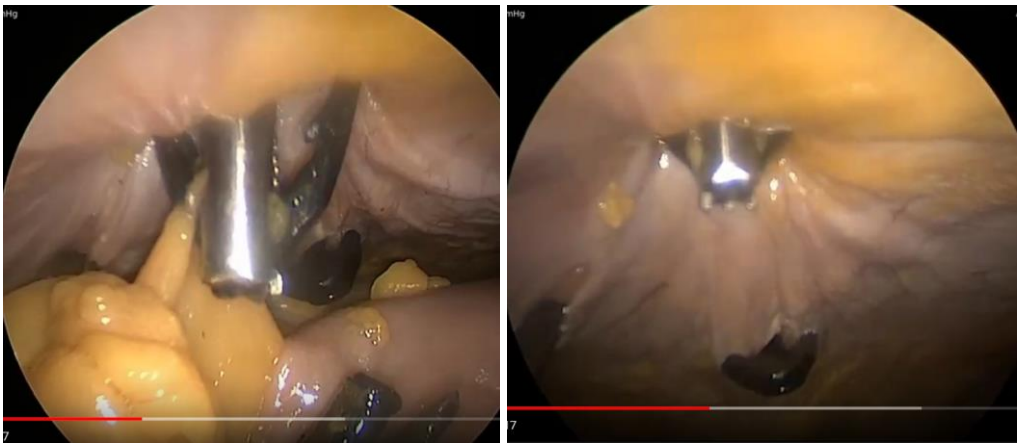


Figure 96: Delivery of TSCC into Cadaver Tissue.

4.4 Short Chronic Animal Study Results

4.4.1 Animal Study Results

Three animal chronic animal studies were conducted at the RRC. Each of the three pigs were kept alive for seven days before being euthanized. From the three animals, Figure 97 shows the histogram of the surgery outcomes. In the first pig from the

study, two surgeons took turns using the device. For consistency, for the second two pigs, only one surgeon from the first study delivered the TSCC.

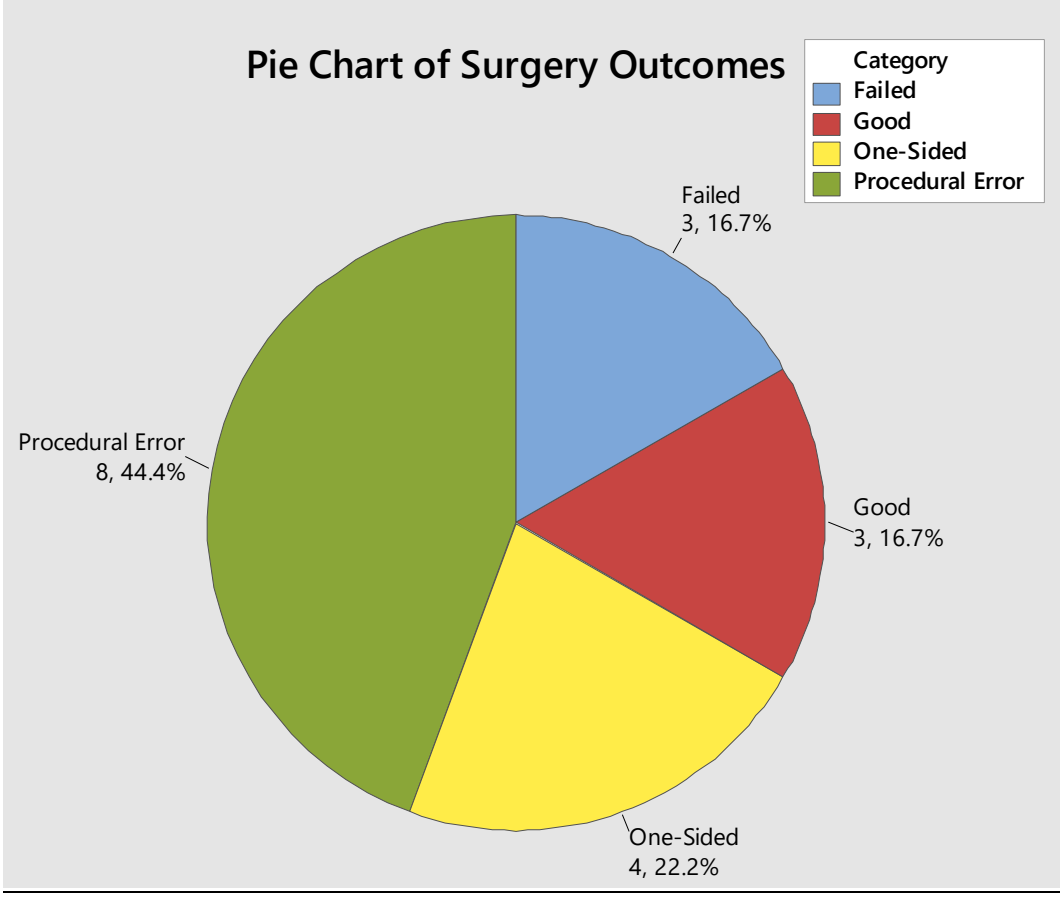


Figure 97: Pie Chart of Surgery Outcomes in Chronic Animal Study.

Three devices resulted in good successful plugs. Four devices had only one arm pierce the tissue. Eight devices resulted in a procedural error when inserting/delivering the device into the tissue. These procedural errors were classified as instances that the device slipped during delivery into the tissue, the surgeon mentioned that “he/she didn’t think they had applied enough force to deliver the device, or the device was jammed in the device applicator after delivery and the surgeon had to break the device to free the applicator. Three devices had a successful delivery. Figure 98 shows the outcomes from necropsy.

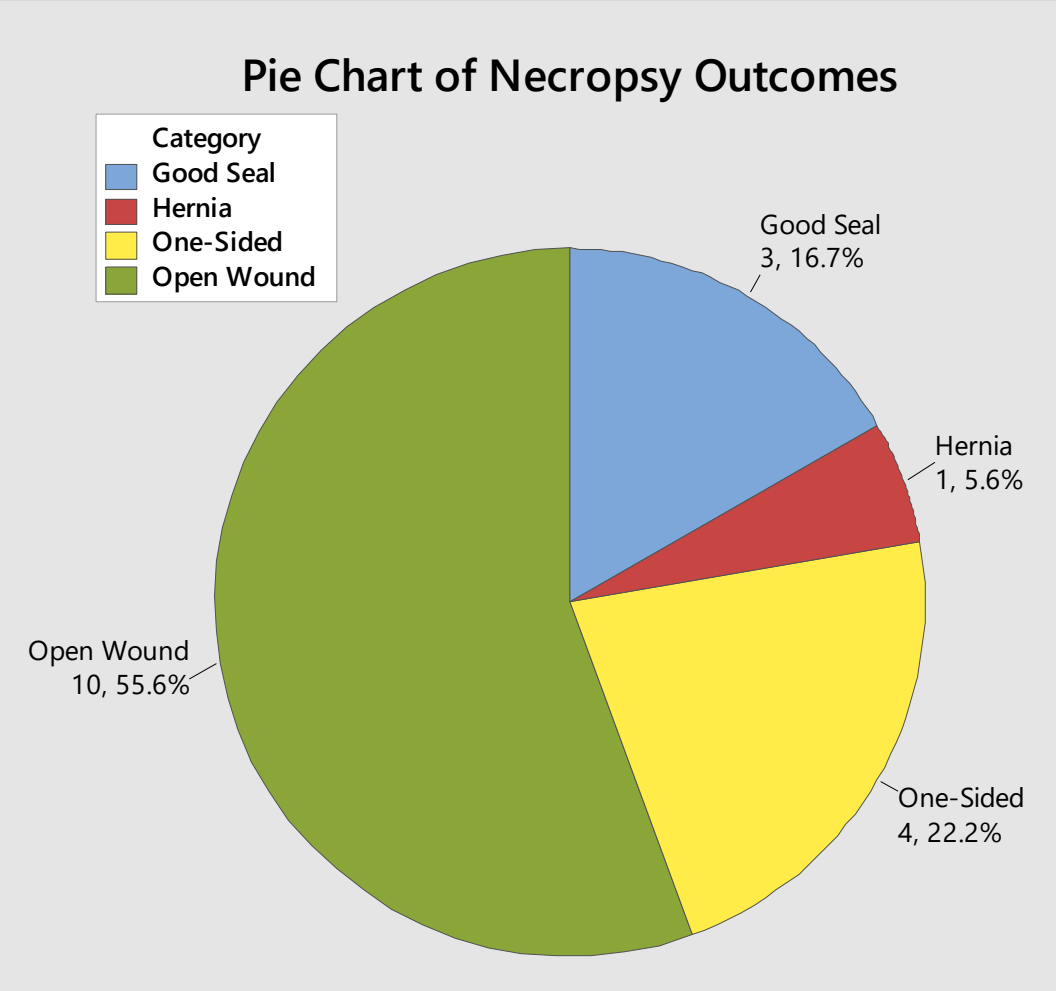


Figure 98: Pie Chart of Necropsy Outcomes in Chronic Animal Study.

Three devices had successful retention in the tissue after seven days, four of them resulted in just one arm stem remaining in tissue after seven days, ten trocar wounds were open and did not have a device penetrating, and one trocar wound herniated displaying the bulging of tissue through the open trocar wound. There weren't hand-held force gauge measurements during the animal trials. Therefore, it was difficult to determine the force at which the devices failed to penetrate the pig tissue and the peak force that the surgeon felt like he wasn't pulling hard enough. This information would have been necessary to perform further analysis of the devices that resulted in procedural errors

during surgery. Figure 99 through Figure 103 show examples of the categories the necropsy results were grouped in.

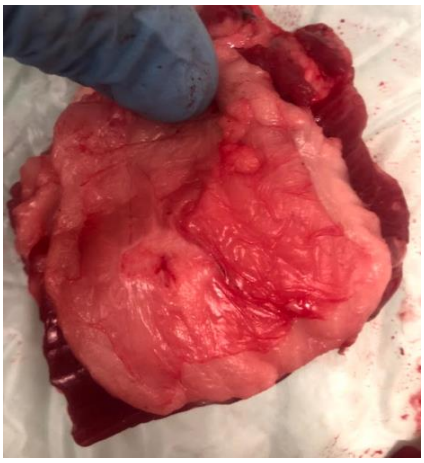


Figure 99: Example of Open Trocar Wound (was not properly plugged) Found in Necropsy.

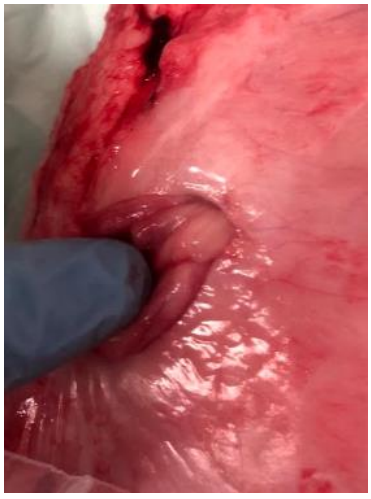


Figure 100: Example of Herniated Trocar Wound Found in Necropsy.

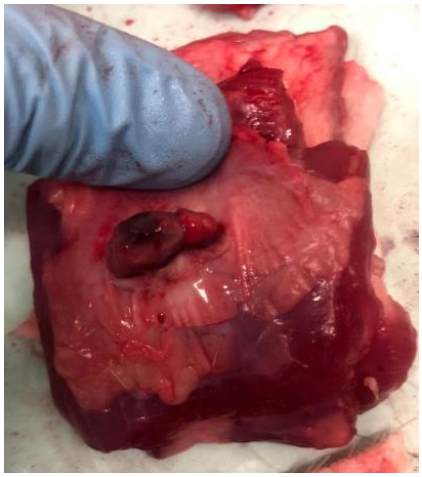


Figure 101: Example of Successful TSCC Found in Necropsy.

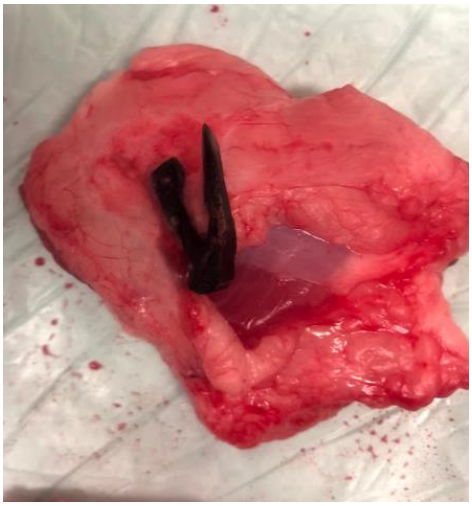


Figure 102: Example of TSCC That Only Had One Arm Penetrate Tissue Found in Necropsy.

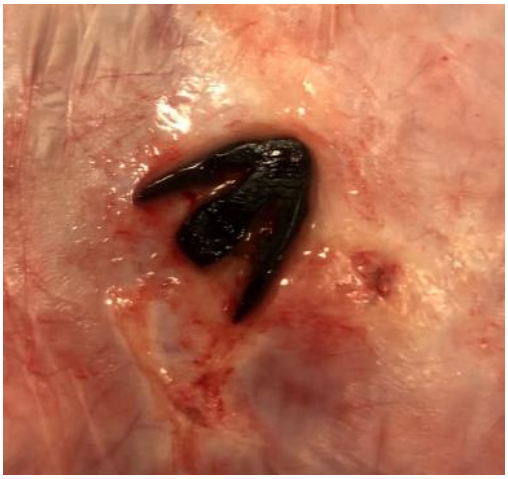


Figure 103: Example of TSCC that had been encompassed by peritoneal tissue (Open Wound).

4.4.2 Histological Findings

In the study, the harvested specimens from the animal study were shipped for histology. The goal of histology was to qualify/compare the presence of new collagen fibers near the incision site, the implanted device, healing around the wound, and get an overall assessment of the biocompatibility of PLA devices in live tissue. Devices found in the three pigs that displayed a good seal, hernia, one side penetration of the device, biodegradation were sent in for histology along with one specimen from each animal that recovered by normal healing and no tissue penetration (as a control). Figure 103 shows a diagram from the list of instructions that were sent to histology for the preparation of slides.

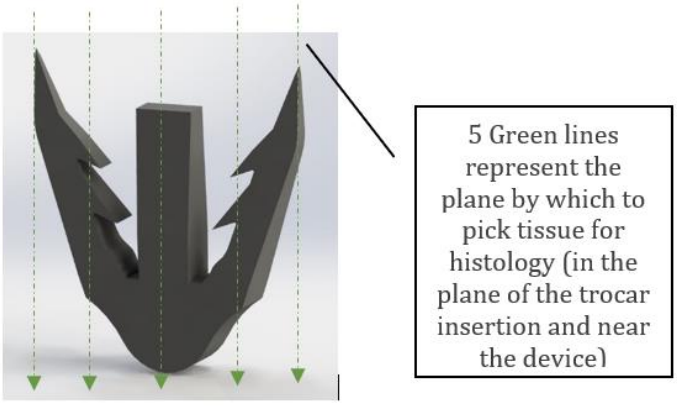


Figure 104: Diagram from Histology Instructions.

A total of 13 of the 18 collected specimens were sent for slide preparation with trichrome blue staining. Five slides were prepared for each specimen at varying levels of depth in the tissue. From the prepared slides a pathologist, analyzed the slides and annotated the healing progression and the cellular findings. The pathologist was given samples that did not have a trocar closure clip as controls (Figure 98) to compare the histological findings.

The samples submitted can be categorized to samples that had one arm of a device penetrate and hold in the porcine tissue (Figure 102), had resulted in a herniation of omental tissue (Figure 101), had been encompassed by the peritoneum (Figure 103), and had a device that successfully plugged the trocar wound site (Figure 101). From the samples that resulted in successful trocar wound closure, the pathologist wrote: “The implant site demonstrates layers of muscle tissue and connective tissue with a core region of collagen proliferation interspersed with neutrophils, macrophages and scattered multinucleated giant cells. Deep in the tissue is a dense aggregation of collagen interspersed with foreign material associated with multinucleated giant cells and macrophages. The material in the multinucleated giant cells and macrophages is interpreted as implant material that is undergoing phagocytosis. There are several foci where the multinucleated cells with foreign material are outside the collagen aggregation.” Later in his reports, the pathologist commented on that “there is no suggestion of toxicity or infection in these sites” of all the sites altogether.

Figure 105 shows the slide of sample in which a device successfully plugged the trocar closure site. From the slide, the pathologist notes that the “Granulation tissue and fibrosis are stained blue with Masson's. The dark blue is likely existing connective tissue stroma. The light blue is developing granulation tissue or fibrosis---this occurs during healing.” Figure 106 shows the giant multinucleated cells and the implant material being phagocytized.

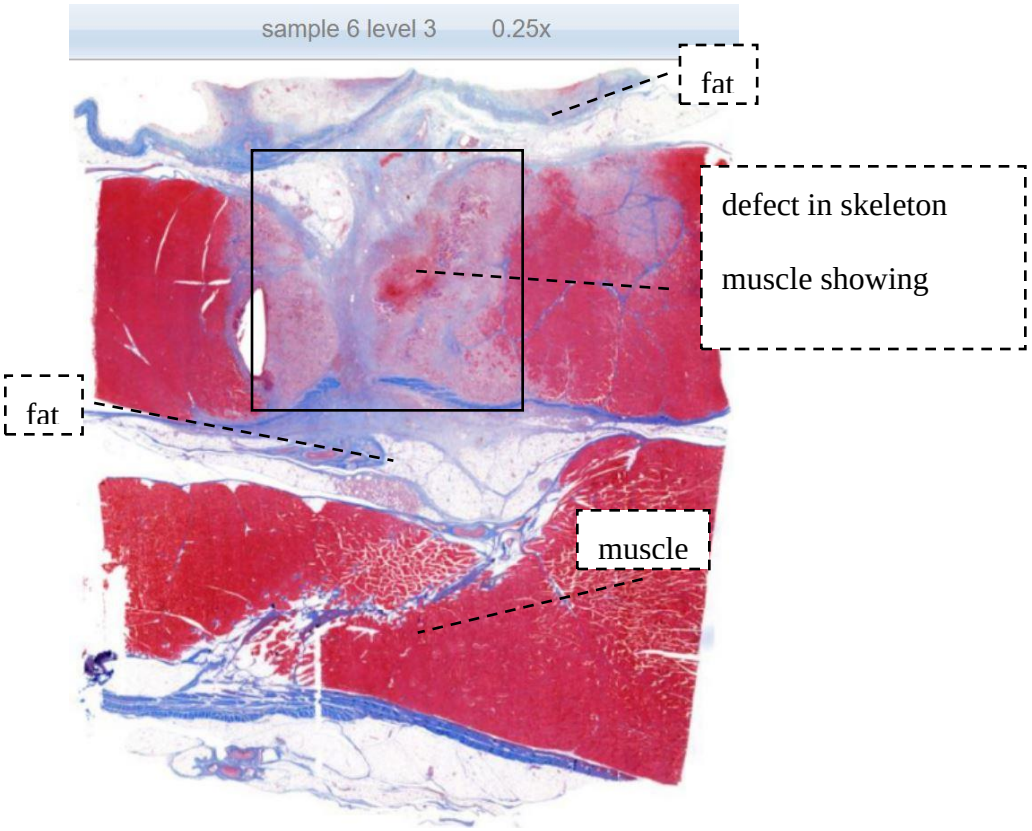


Figure 105: Picture of Slide from Pathologist.

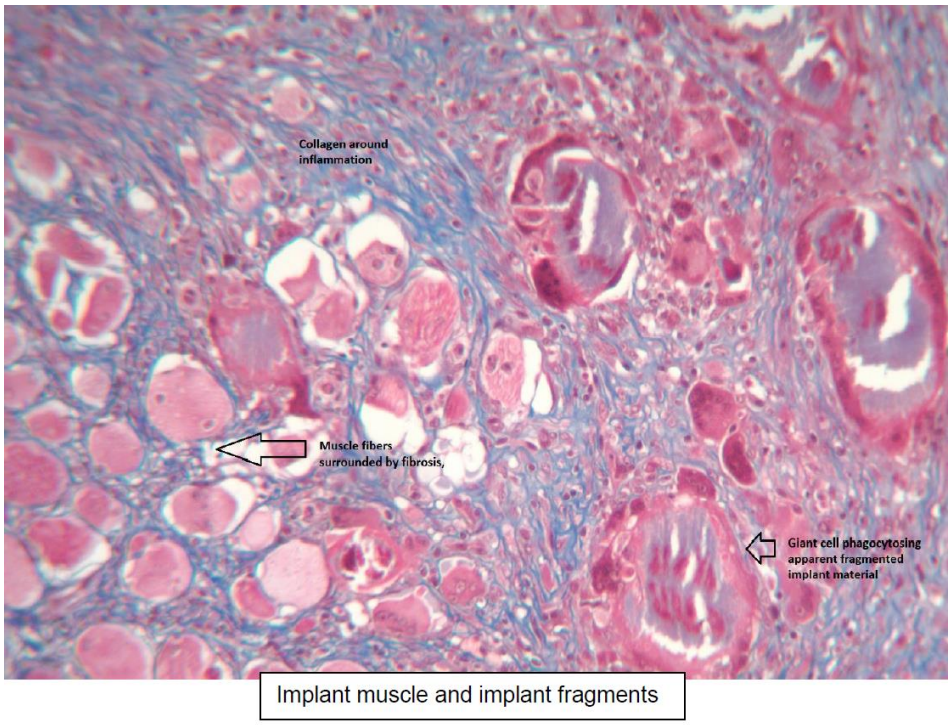


Figure 106: High Power Image of Cellular Interaction with Degenerating Foreign Material.

V. DISSCUSSION & CONCLUSION

The primary objective of this MEng thesis was to fabricate and validate a device that proves the concept of using a biocompatible PLA clip to plug and seal a trocar wound site preventing an opportunity for postoperative herniation.

The devices developed and tested in this study prove the concept that a PLA clip can be used to plug and seal a 12mm trocar wound site preventing an opportunity for postoperative herniation.

A testing of PLA devices in cadaver tissue show that the TSCC clips are flexible enough to travel through a 12mm trocar without plastic deformation, can penetrate cadaver tissue and plug a trocar wound, and are rigid enough to be retained in the tissue.

From chronic animal studies it is shown that the PLA device used in testing is non-toxic and exhibits appropriate biocompatibility for the scope of this device. There are factors that could have limited the results of this thesis. After the second design update of the TSCC with a manual taper on the device arms, the repeatability and consistency of the devices decreased. Without having a mold or machinery to shape the tapered design of the TSCC, the results of the studies included an increased variability. Also, not having a specifically designed applicator tool for the devices and having to manually stamp the devices after re-heating the devices created an offset of the arms. The magnitude of this offset could not be predicted and therefore, each TSCC had a vulnerable failure point on one side of the device. While re-heating the stem of the device for stamping, the heat was

not always concentrated onto the stem of the device, therefore, the device arms in some cases were affected.

Due to the weight of the hand-held gauge along with the length and awkwardness of the entire set-up, the measurements during cadaver lab sessions could have been affected. In addition, the hand-held force gauge was creating an unorthodox way to deliver the device into the abdominal wall. Due to the structured way devices were benchtop tested with a load frame, the position in benchtop testing didn't always correlate to the position the device was delivered in the cadaver lab or pig. With the load frame the device was always vertical and, in the cadaver/animal an organic torque was introduced because of the natural curve of the abdominal cavity. This was unmeasurable during the study.

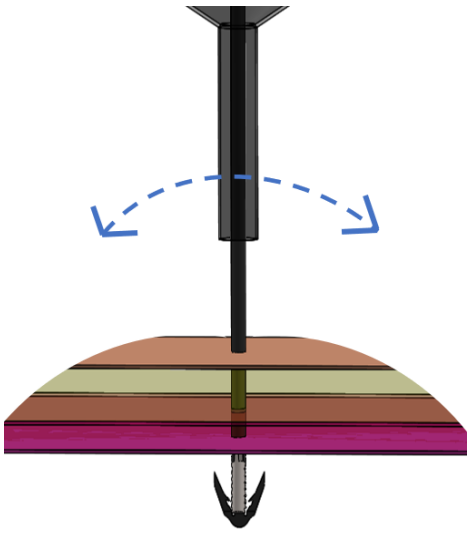


Figure 107: Depiction of the torque generated by a non-perpendicular abdominal cavity.

Lastly, the applicator was a limitation in this study. The applicators used in the latter half of this study were existing laparoscopic tools. The TSCC devices had to be deformed and manipulated to conform to the distal design and the grip of the lap tool applicators compromising the integrity of the PLA. Also, the length of the applicators was too long and awkward during device delivery creating torque on the device arms. If the applicator was custom designed, these limitations created could have been mitigated.

In summary, a PLA trocar closure clip was used to plug and seal a 12mm trocar wound preventing postoperative herniation. However, the design and manufacturing of the device is critical along with the applicator used to deliver the device. From the results obtained in the chronic animal trials, the theory of this proposal was validated. Although, the results were not consistent, the concept of using plugging a trocar wound site closed with a PLA clip was shown to be effective. Of the 11 open wounds from the chronic animal trial, one open wound resulted in herniation of tissue. Post-operative herniation is a legitimate risk that can be mitigated with proper blocking of the trocar site.

For the future of the work performed in this thesis, a couple recommendations can be made. There is a need to design an injection mold for the updated designed TSCC instead of using 3D printing. This method will decrease the amount of waste in the manufacturing of the devices and will allow the PLA to be formed and then cooled into the exact shape with the taper intended along with the proximal pattern so that the device is compatible with the applicator. After the manufacturing steps for the TSCC are completely mechanized, follow-up animal labs should be conducted to show efficacy of

the manufacturing process and the TSCC. In addition, a custom applicator device should be designed for the TSCC. This will deter users of the device from using their own applicator with the TSCC which would minimize user errors. If the applicator is designed specifically for the TSCC both can be testing in conjunction for efficacy. The critical design components of the TSCC are the length of the shaft, distal grip design, and the releasing mechanism of the applicator.

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VII. VITA

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Master of Engineering in Bioengineering — Expected May 2019
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R&D Robotics Co-op — 01/17 – 05/17
Ethicon Endo-Surgery
Cincinnati, OH

R&D Product Management — 05/16 – 08/16
Ethicon Endo-Surgery
Cincinnati, OH

R&D Front-End Energy — 08/15 – 12/15
Ethicon Endo-Surgery
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EDR Management — 05/14 – 05/15
UofL Resident Assistant
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Cardinal Host — 08/14 – 5/17
UofL President's Office Ambassador
Louisville, KY

LEADERSHIP EXPERIENCE

RSO President 12/15 – 12/16
Indian Student Association
Louisville, KY

Fraternity President 12/15 – 12/16
Pi Kappa Alpha
Louisville, KY

Honors Greek Society President 12/15 – 12/16
Order of Omega
Louisville, KY

Team Leader 10/15 – 02/17
raiseRED Dance Marathon
Louisville, KY

Director of Public Relations 01/15 – 12/15
Speed School Student Council
Louisville, KY

RSO President 08/13 – 05/14
Freshman Speed School Council
Louisville, KY

VOLUNTEER EXPERIENCE

Elementary Student Tutor/Mentor 2014 – 2018
Cochran Elementary Cardinal Club
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HONORS & AWARDS

Fraternity Man of the Year May 2017
UofL Greek Life Awards
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Most Outstanding Junior May 2016
UofL Student Awards
Louisville, KY

Mr. Ambassador May 2015
REACH Ambassador Program
Louisville, KY

Mr. Lead May 2014
Freshman LEAD Program
Louisville, KY

Most Outstanding Freshman May 2014
UofL Student Awards
Louisville, KY

UofL Trustee's Scholarship 08/13 – 05/17
JB Speed School of Engineering

Dean's List (x7) 12/13, 12/14, 2015, 2016, 2017
JB Speed School of Engineering

Governor's Scholarship Program Summer 2012
Murray State University

ABSTRACTS & PRESENTATIONS

Research! Louisville 10/18
Suture-Less Trocar Site Closure for Postoperative Hernia Prevention following Laparoscopic Surgery
Hares A. Patel, B.S.[1], Daniel S. Metzinger, M.D.[2], Robert S. Keynton, Ph.D.[1], Dakota J. Waldecker, B.S.[1]
Departments of Bioengineering[1] and Surgery[2]
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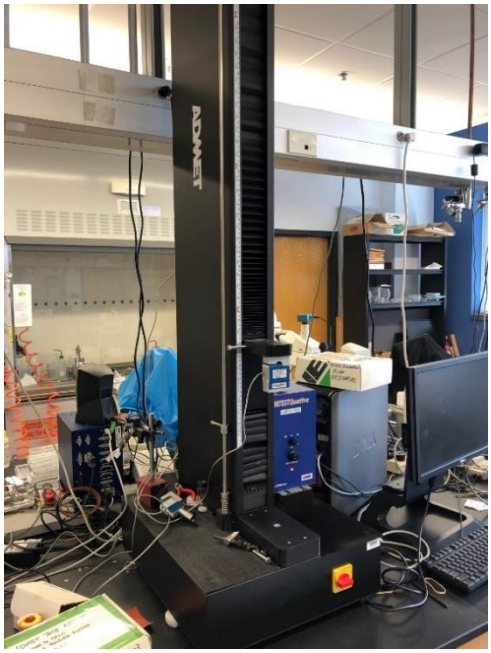
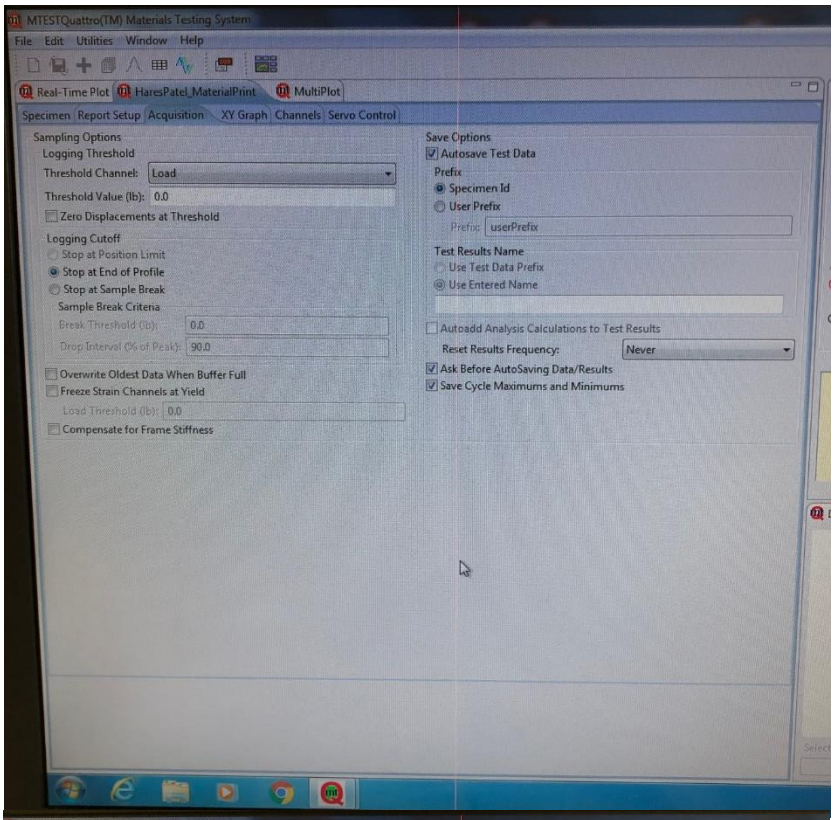
VIII. APPENDIX

6.1 MTestQuatro

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Logging Cutoff
Stop at Position Limit
Stop at End of Profile
Stop at Sample Break
Sample Break Criteria
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Freeze Strain Channels at Yield
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Save Options
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Prefix
Specimen Id
User Prefix
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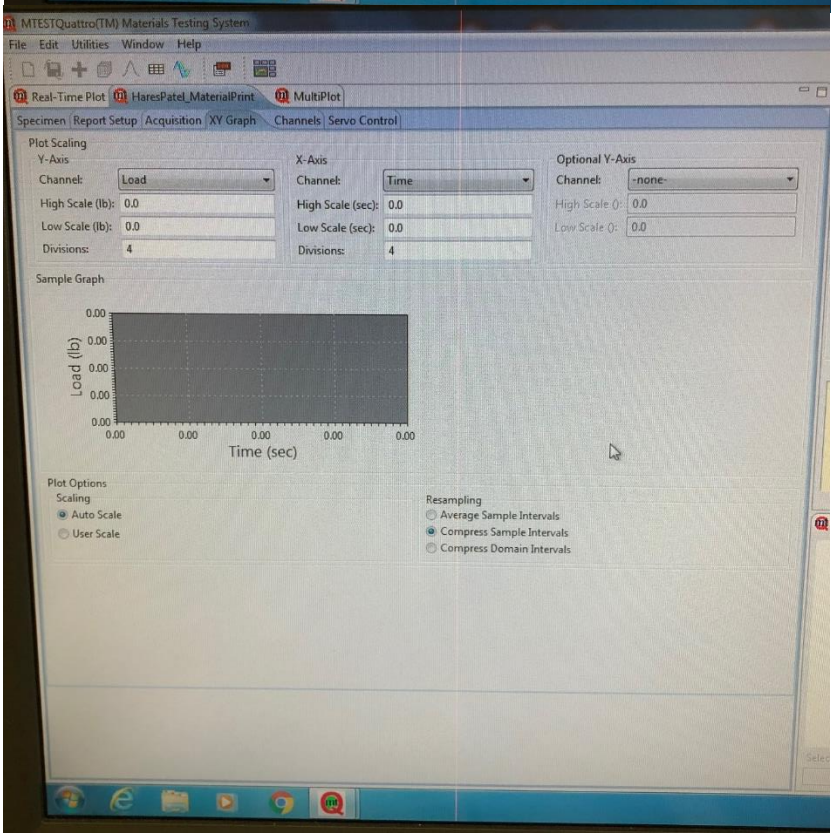
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MultiPlot
Specimen Report Setup Acquisition XY Graph Channels Servo Control
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Low Scale (lb): 0.0
Divisions: 4
X-Axis
Channel: Time
High Scale (sec): 0.0
Low Scale (sec): 0.0
Divisions: 4
Optional Y-Axis
Channel: -none-
High Scale (): 0.0
Low Scale (): 0.0
Sample Graph
Load (lb)
0.00
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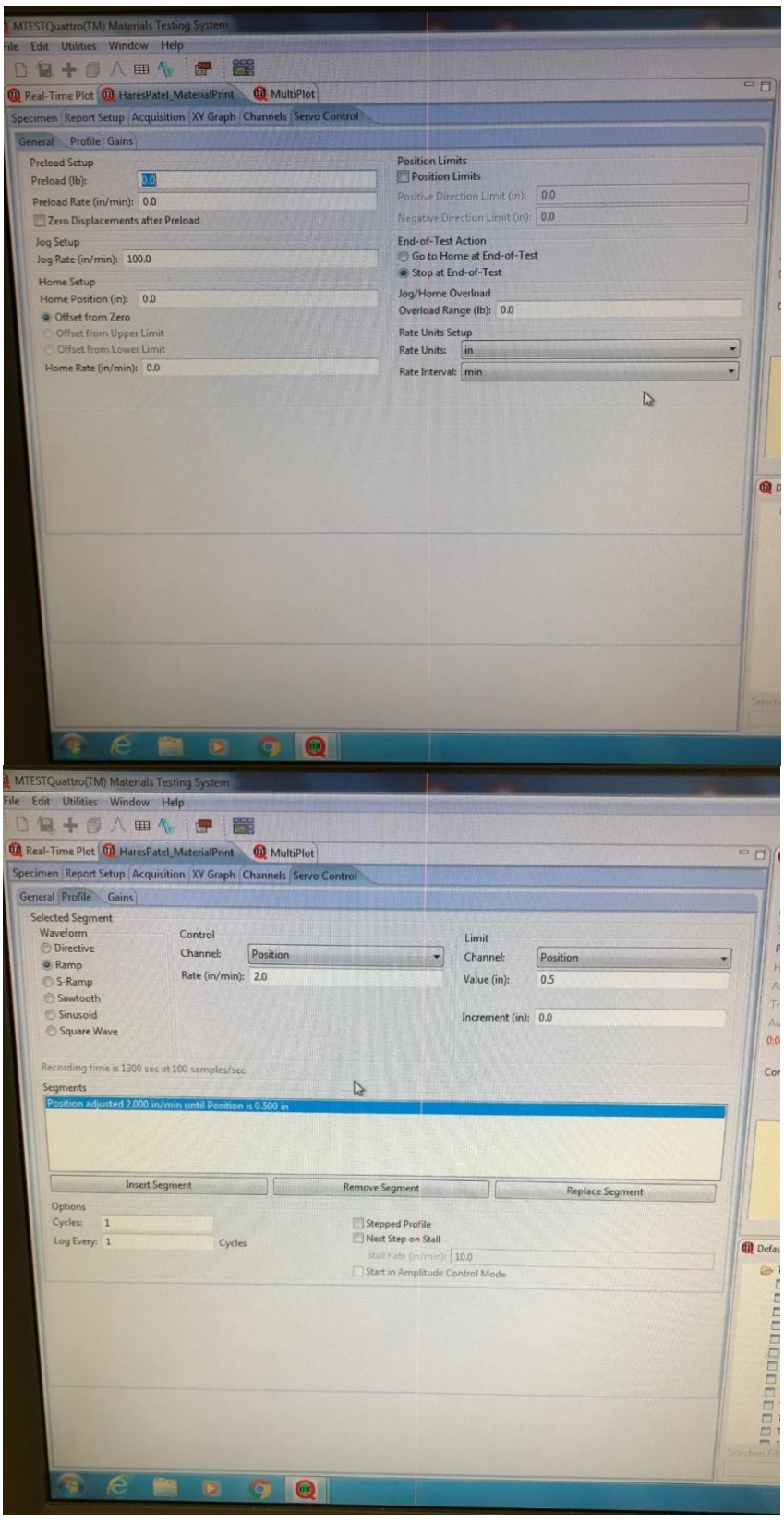
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Jog Setup
Jog Rate (in/min): 100.0
Home Setup
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Offset from Zero
Offset from Upper Limit
Offset from Lower Limit
Home Rate (in/min): 0.0
Position Limits
Position Limits
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Negative Direction Limit (in): 0.0
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Go to Home at End-of-Test
Stop at End-of-Test
Jog/Home Overload
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Rate Units Setup
Rate Units: in
Rate Interval: min
MTESTQuattro(TM) Materials Testing System
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Real-Time Plot
HaresPatel_MaterialPrint
MultiPlot
Specimen Report Setup Acquisition XY Graph Channels Servo Control
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Directive
Ramp
S-Ramp
Sawtooth
Sinusoid
Square Wave
Control
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Rate (in/min): 2.0
Limit
Channel: Position
Value (in): 0.5
Increment (in): 0.0
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Replace Segment
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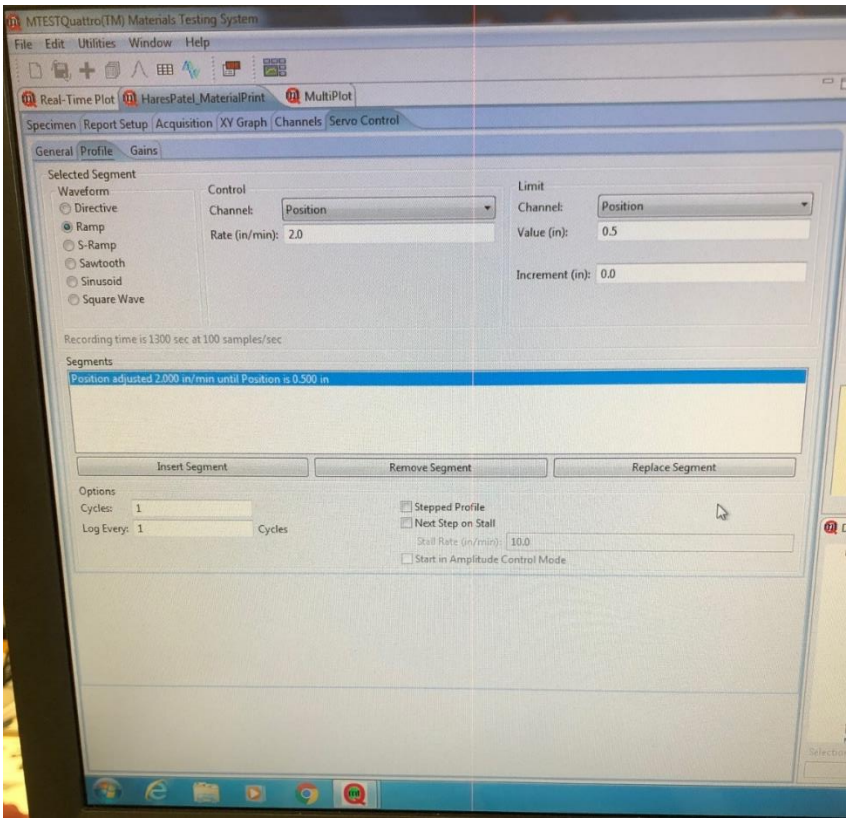

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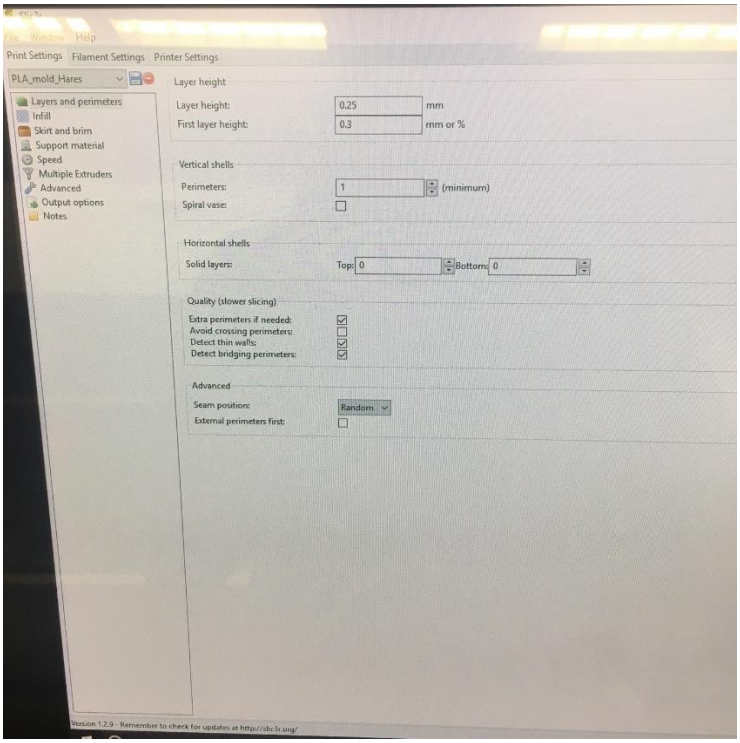

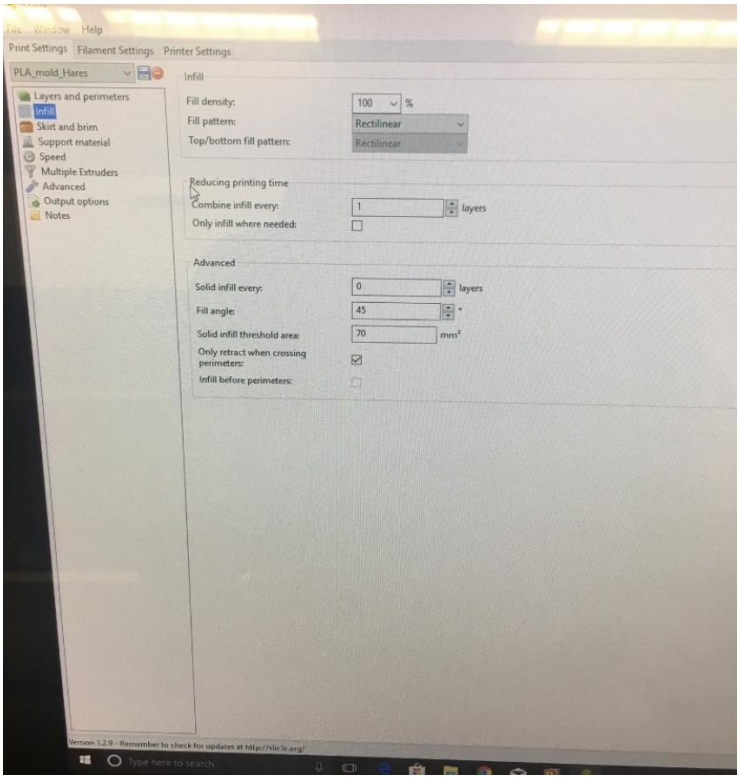
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Skirt and brim
Support material
Speed
Multiple Extruders
Advanced
Output options
Notes
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%
Fill pattern:
Rectilinear
Top/bottom fill pattern:
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Reducing printing time
Combine infill every:
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layers
Only infill where needed:
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Solid infill every:
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°
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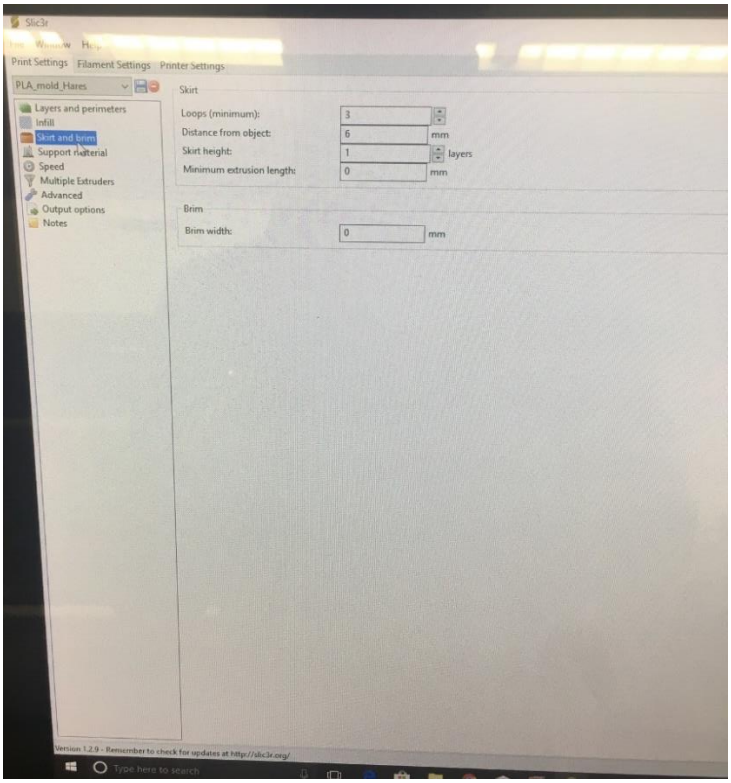
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Speed
Multiple Extruders
Advanced
Output options
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Loops (minimum):
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Distance from object:
6
mm
Skirt height:
1
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Brim
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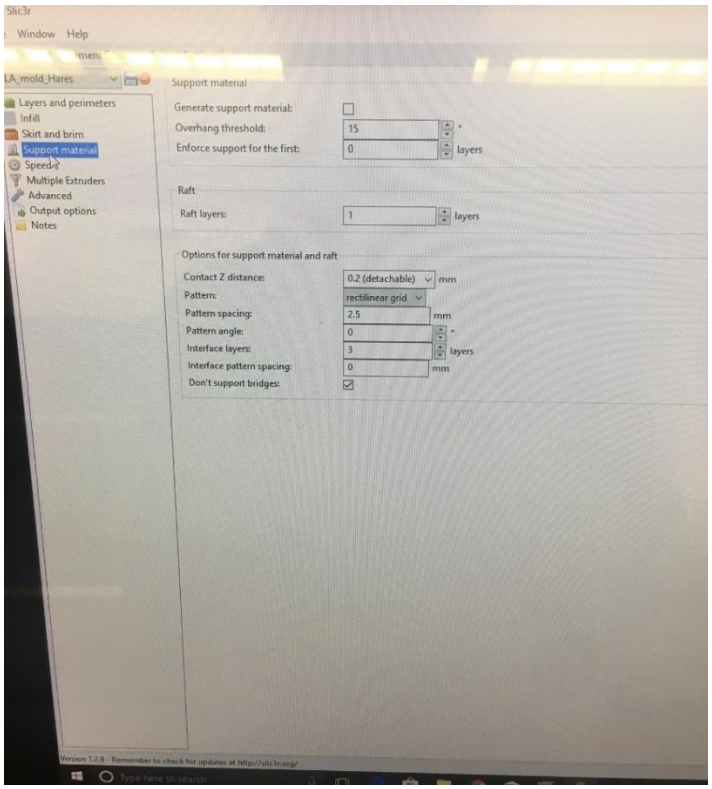
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Options for support material and raft
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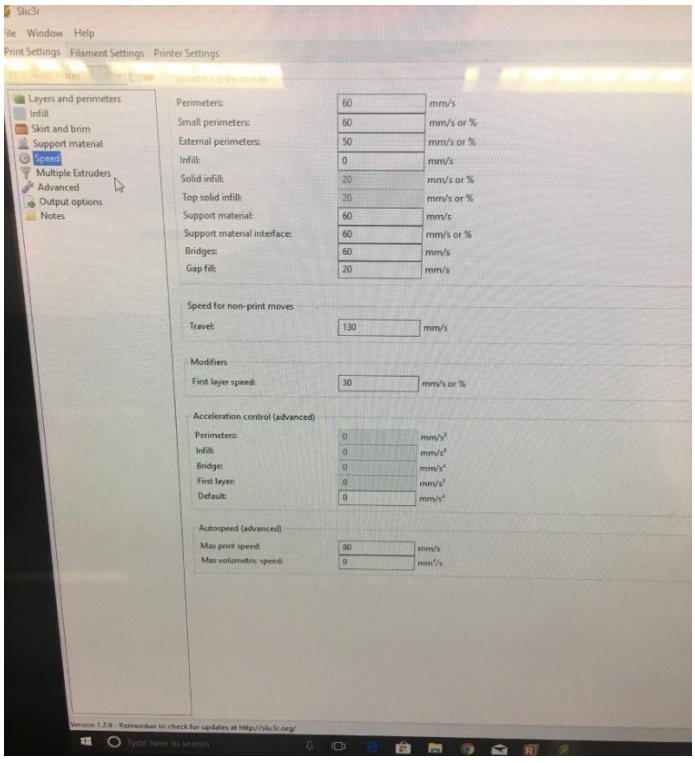
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mm/s
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mm/s or %
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Top solid infill:
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Support material:
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Support material interface:
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Bridges:
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Gap fill:
20
mm/s
Speed for non-print moves
Travel:
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mm/s
Modifiers
First layer speed:
30
mm/s or %
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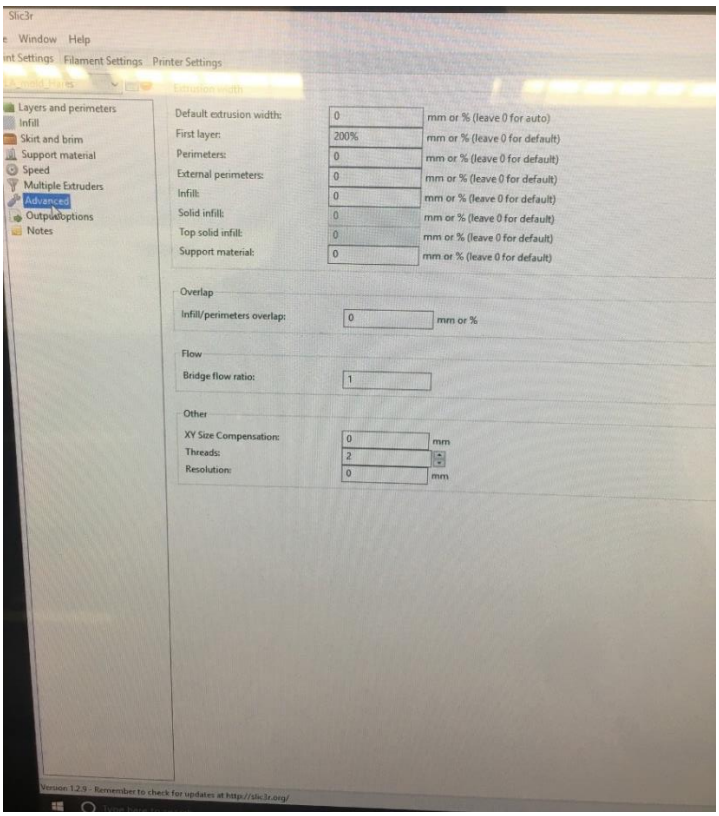
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Window Help
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Layers and perimeters
Infill
Skirt and brim
Support material
Speed
Multiple Extruders
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Output options
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Default extrusion width: 0 mm or % (leave 0 for auto)
First layer: 200% mm or % (leave 0 for default)
Perimeters: 0 mm or % (leave 0 for default)
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Infill: 0 mm or % (leave 0 for default)
Solid infill: 0 mm or % (leave 0 for default)
Top solid infill: 0 mm or % (leave 0 for default)
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Overlap
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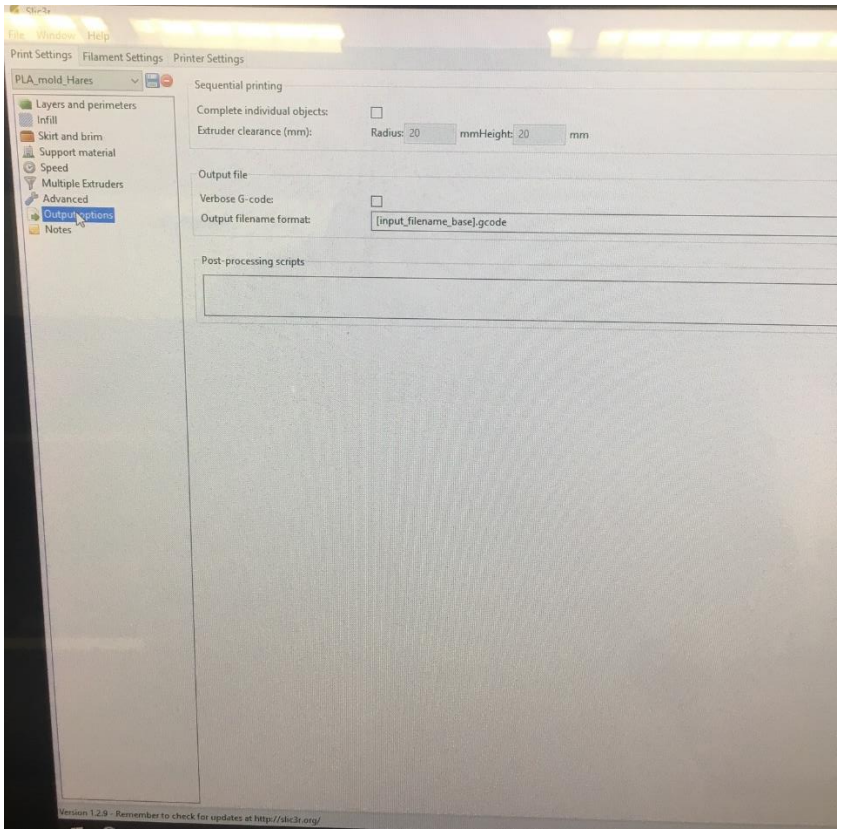
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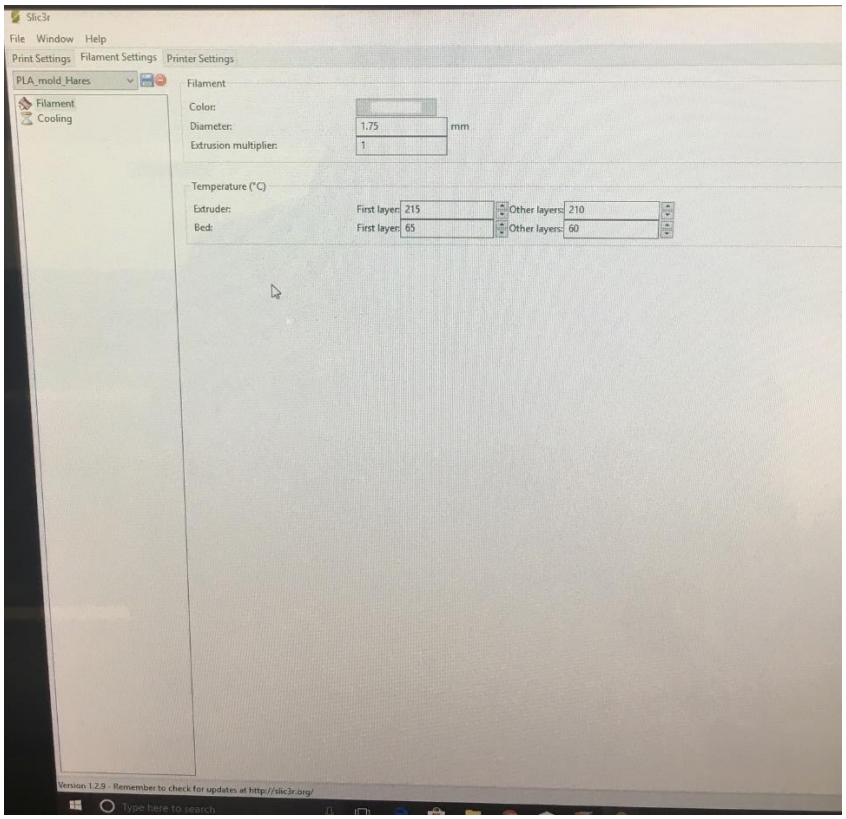
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Cooling
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Temperature (°C)
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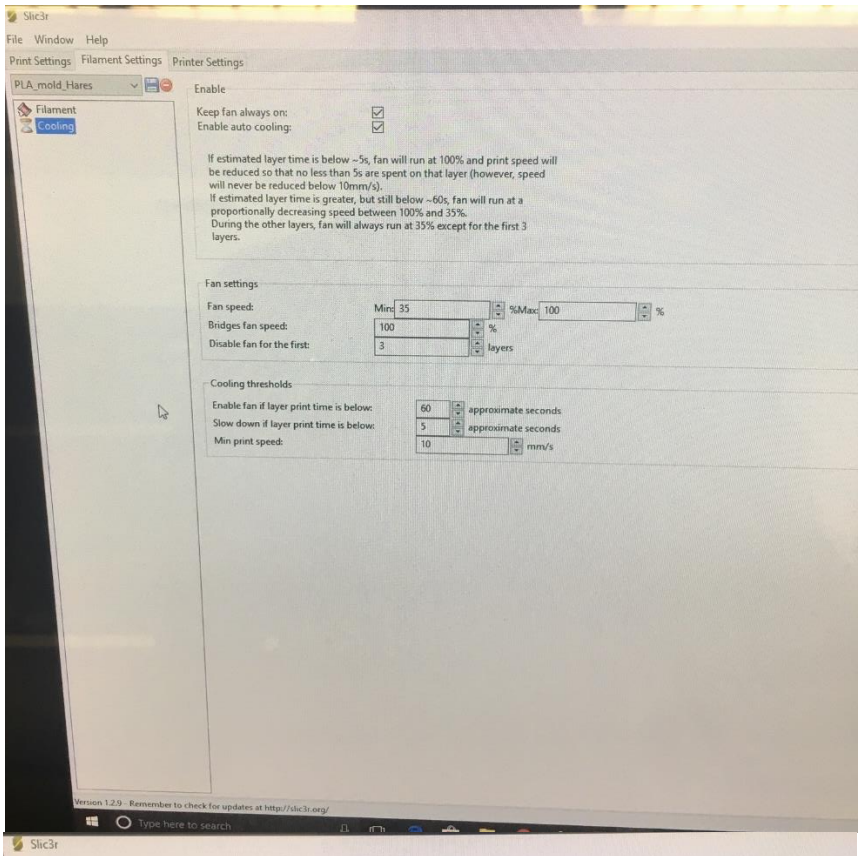
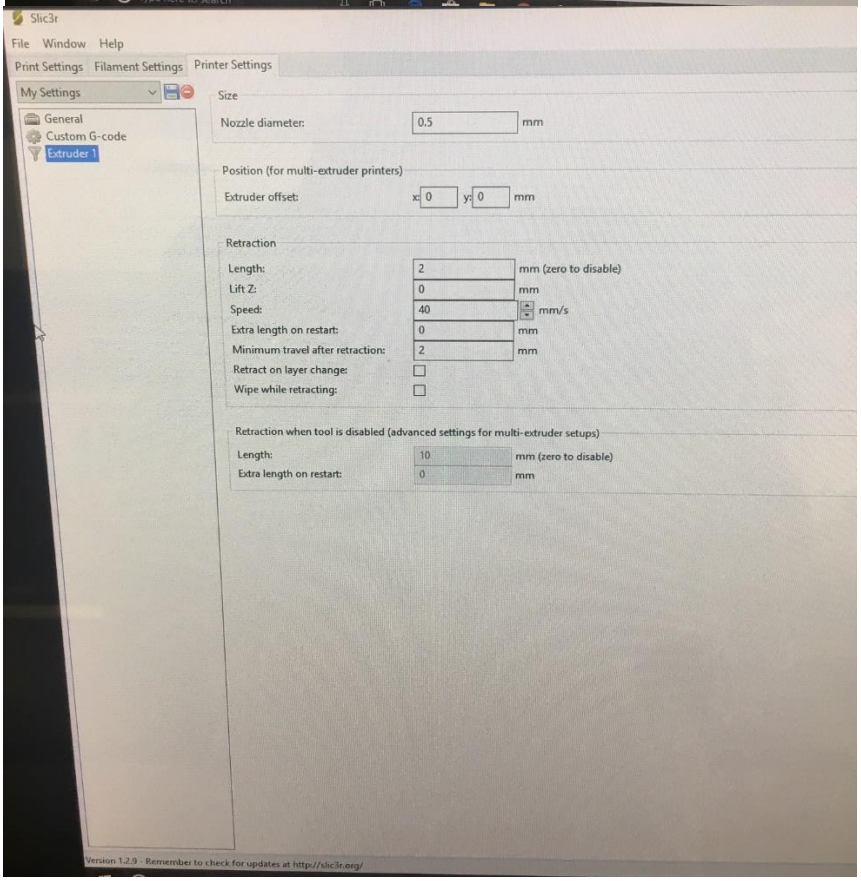
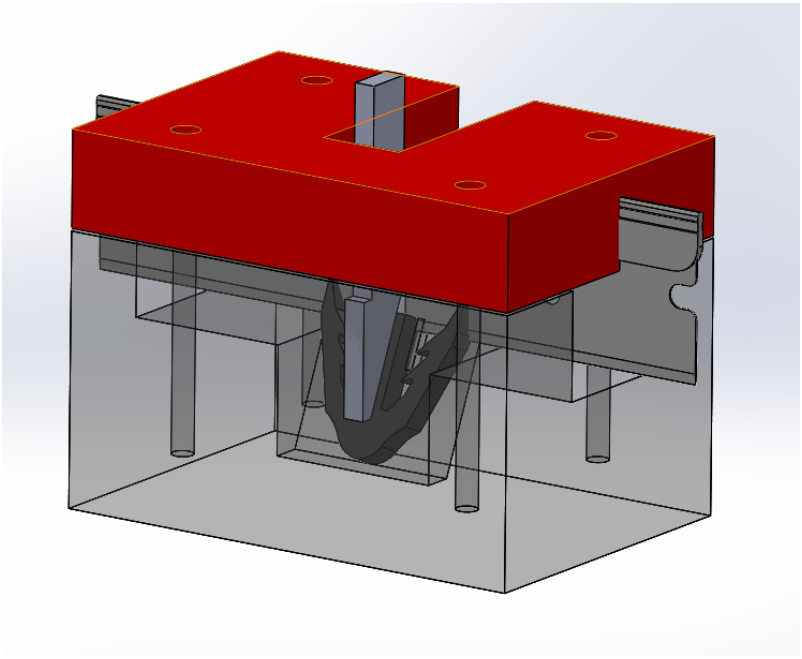
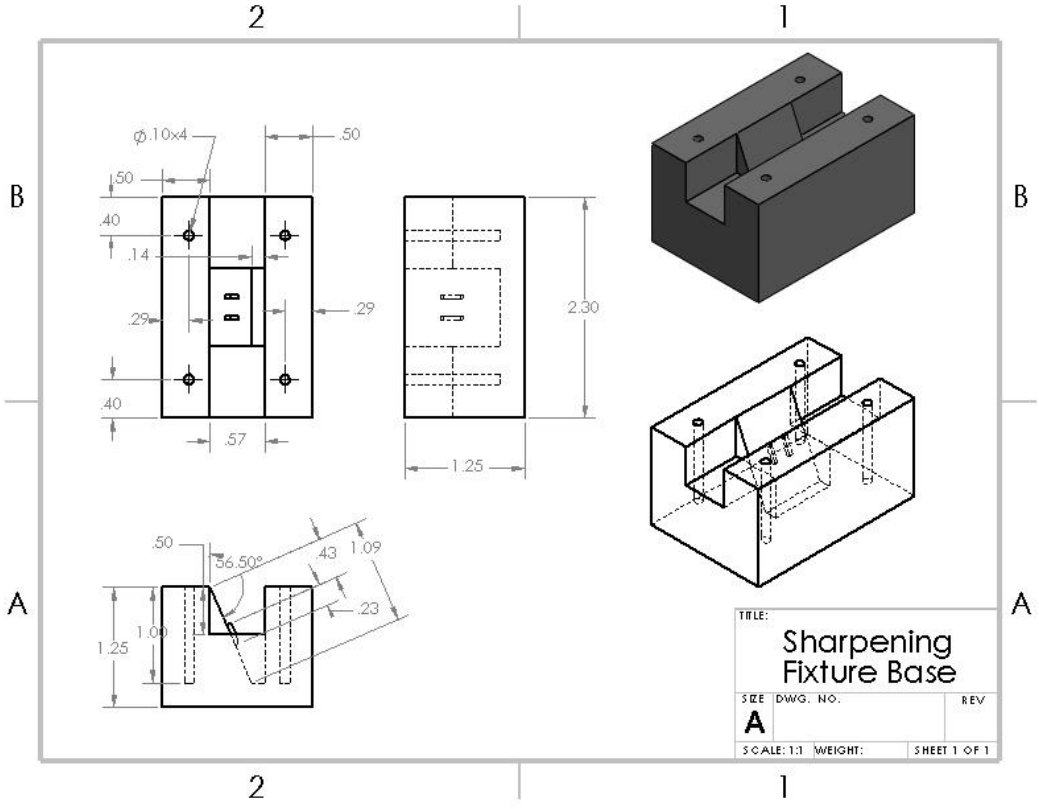
Bed: First layer: 65 Other layers: 60
Version 1.2.9 - Remember to check for updates at http://slic3r.org/
Type here to search

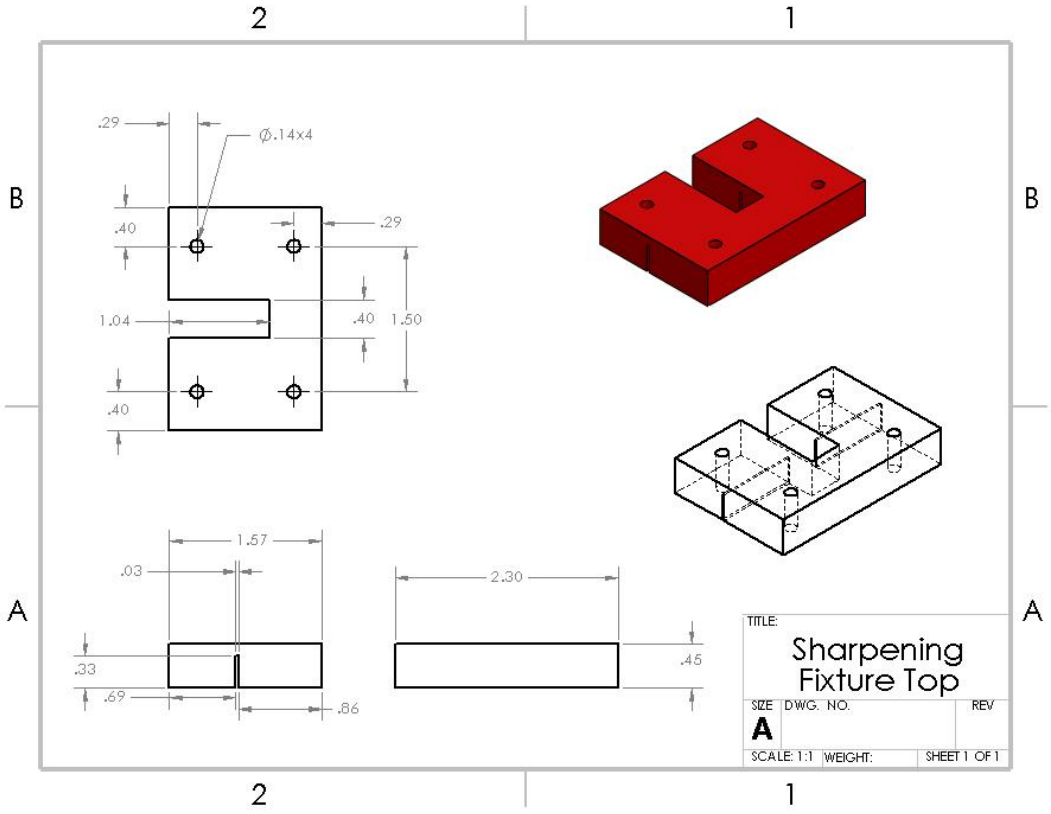

Slic3r
File Window Help
Print Settings Filament Settings Printer Settings
PLA_mold_Hares
Filament
Cooling
Enable
Keep fan always on:
Enable auto cooling:
If estimated layer time is below ~5s, fan will run at 100% and print speed will be reduced so that no less than 5s are spent on that layer (however, speed will never be reduced below 10mm/s).
If estimated layer time is greater, but still below ~60s, fan will run at a proportionally decreasing speed between 100% and 35%.
During the other layers, fan will always run at 35% except for the first 3 layers.
Fan settings
Fan speed:
Min: 35
%Max: 100
%
Bridges fan speed:
100
%
Disable fan for the first:
3
layers
Cooling thresholds
Enable fan if layer print time is below:
60
approximate seconds
Slow down if layer print time is below:
5
approximate seconds
Min print speed:
10
mm/s
Version 1.2.9 - Remember to check for updates at http://slic3r.org/
Type here to search

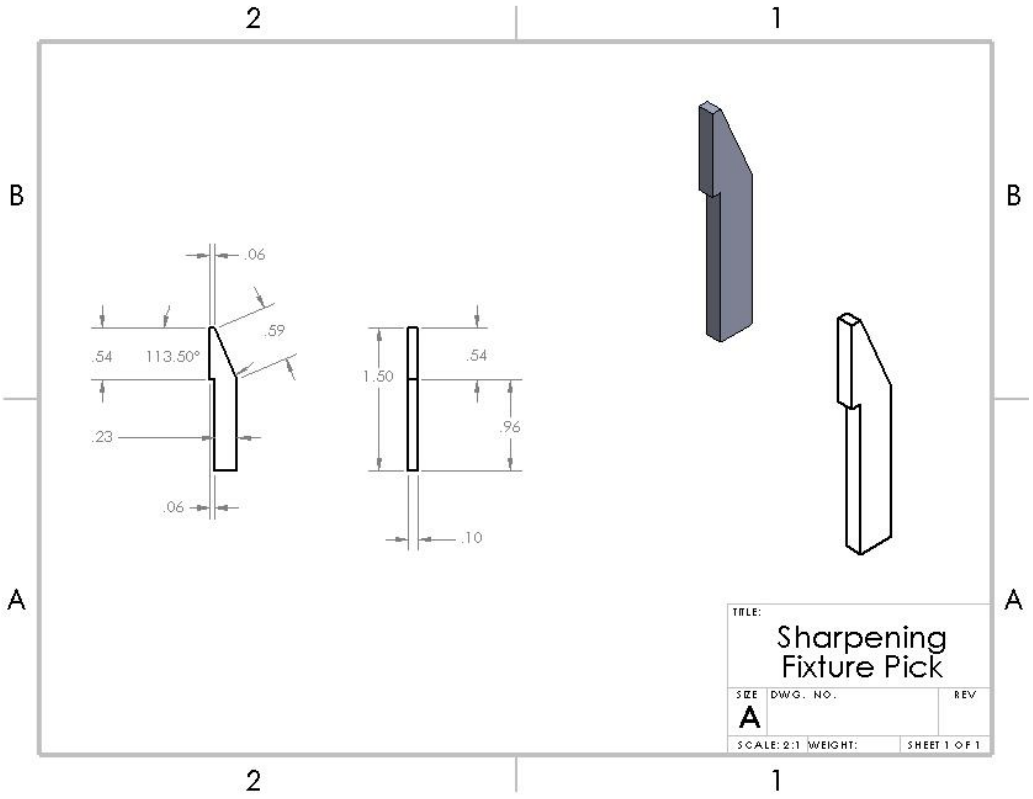

Slic3r
File Window Help
Print Settings Filament Settings Printer Settings
My Settings
General
Custom G-code
Extruder 1
Size
Nozzle diameter:
0.5
mm
Position (for multi-extruder printers)
Extruder offset:
x: 0
y: 0
mm
Retraction
Length:
2
mm (zero to disable)
Lift Z:
0
mm
Speed:
40
mm/s
Extra length on restart:
0
mm
Minimum travel after retraction:
2
mm
Retract on layer change:
Wipe while retracting:
Retraction when tool is disabled (advanced settings for multi-extruder setups)
Length:
10
mm (zero to disable)
Extra length on restart:
0
mm
Version 1.2.9 - Remember to check for updates at http://slic3r.org/

6.3 Sharpening Device Fixture Drawings

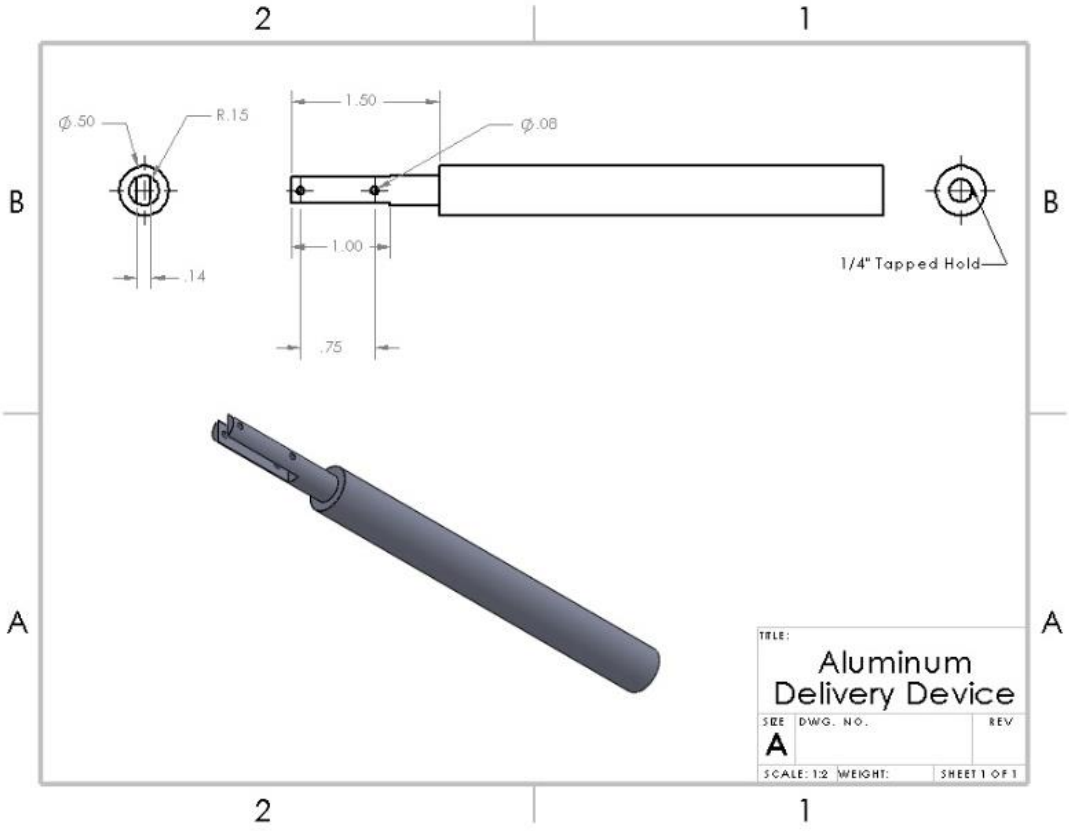





2
1
B
A
.29
Ø.14x4
.40
.29
1.04
.40
1.50
.40
1.57
.03
.33
.69
.86
2.30
.45
TITLE:
Sharpening Fixture Top
SIZE
A
DWG. NO.
REV
SCALE: 1:1
WEIGHT:
SHEET 1 OF 1



6.4 First Applicator Drawings


2
1
B
A
Ø.50
R.15
.14
1.50
Ø.08
1.00
.75
1/4" Tapped Hold
TITLE:
Aluminum
Delivery Device
SIZE
A
DWG. NO.
REV
SCALE: 1:2
WEIGHT:
SHEET 1 OF 1

6.5 IACUC Chronic Animal Study Application

IACUC Application (Version 1.3)

1.0 General Information

*Please enter the full title of your study:		
Suture-Less Trocar Site Closure Clip & Herniation Prevention Device		
*Please enter the Short Study Title you would like to use to reference the study:		
Trocar Site Closure Clip * This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.		

2.0 Add Department(s)

2.1 List the departments associated with this study. Add the Principal Investigator's department as the PRIMARY DEPARTMENT. For research conducted at a Norton facility add: Norton Healthcare. For research conducted at a Jewish Hospital/KyOne facility (e.g. Frazier, St Mary's, etc) add: Ky One Health. For research conducted at University Hospital/James Graham Brown Cancer Center add: University Hospital:

Primary Dept?	Department Name
○	**U of L** - *10* - Admin Support Services
◉	**U of L** - *29* - Spd-Bio-Engineering

3.0 Assign key study personnel (KSP) access to the project

3.1 *Please add a Principal Investigator for the study:

Metzinger, Daniel S, M.D.

3.2 In this section, please add any project personnel that needs to have access to the submission or will need to approve the submission. In the case of the Undergraduate Research Symposium, your mentor and co-authors would be included in this section.

A) Additional Investigators

Keynton, Robert S
Co-Investigator
Patel, Hares A
Co-Investigator

B) Research Support Staff

3.3 *Please add a Study Contact. The Study Contact(s) will receive all important system notifications along with the Principal Investigator. If applicable, please add Kentucky One

Health, Norton Healthcare or UMC Research as a study Contact. Adding someone here does not add them as study personnel.

Patel, Hares A

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. If applicable, please add Kentucky One Health, Norton Healthcare or UMC Research as a study Contact.

4.0 IACUC Form Type

4.1 Please indicate the type of form you are submitting

- (•) Live Animals
- ( ) Tissue Only

- **Live Animals** - Use this form if you will be using any live animals at UofL, including description of Core Animal Laboratories.
- **Tissue Only** - Use this form if you will be using ***fresh*** or ***frozen*** (not fixed) tissues, organs, or carcasses obtained from animals outside of UofL or from animals assigned to, and euthanized by, PIs with other IACUC *Proposals*. If you plan to handle live animals in any way, a *Live Animal* form must be used. [Link to Policy]

5.0 Emergency Contacts

5.1 Indicate the Key Study Personnel who will act as emergency contacts

Study Personnel	Phone Numbers
Keynton, Robert A	During Work Hours: 5028026348
	After Hours: 5028026348
Patel, Hares A	During Work Hours: 9146218058
	After Hours: 9146218058

6.0 Welcome Page

6.1

Welcome to

IACUC

@

Louisville

Replacement

Reduction
Refinement
Responsibility

Do I need an IACUC protocol?

For best viewing of form materials, it is recommended that you expand your window as much as possible.

7.0 Proposal Purpose / 3 Year Renewal

7.1 Proposal Purpose

(Check all that apply)

- [x] Research using live animals
- [ ] Teaching and Training
- [ ] Core Animal Laboratory Proposal

Is this a 3-Year Renewal?

( ) Yes (•) No

7.3 Scientific Review and Funding Source(s)

Scientific review has been, or will be, performed by an internal or external review panel before experimentation begins. Select all that apply:

- [ ] Federal Agency
- [ ] State Agency
- [x] Private Foundation
- [ ] U of L Review Panel
- [ ] Industry Sponsor
- [ ] Department Chair or Designee
- [ ] Other

List any funding sources applicable to this Proposal

Grant No.	Sponsor	Title
GB110749B4	Coulter Foundation	Novel Suture-Less Trocar Site Closure & Herniation Prevention Device

8.0 Species to be used in this Proposal (Only ONE Allowed)

8.1 Select species in drop down list below.

Note: If the species you would like to use is not listed, please contact the IACUC Office (IACUC@Louisville.edu, 852-7307) so that it may be added to the form.

Select Species to be used in the Proposal (for Field Study, select "Wild Caught Species")

Pig (Domestic)

8.2 Justification of Selected Species

Give rationale for the selection of this species. In all cases, a "lower" species should be given primary consideration.

Swine were chosen for this project because they are a much closer model to humans in regards to size of abdominal region, weight and physiology. They are able to have laparoscopic procedures performed in the same fashion as those done in humans. Rabbits and rodents are not acceptable due primarily to the size of the abdominal region, there simply isn't enough space to perform an analogous laparoscopic procedure similar to that performed in humans. There were a few noted articles discussing the use of rabbit models for use in analogous studies for infant/pediatric laparoscopic procedures.

8.3 List strains, lines, stocks, breeds, *etc.* in the table below.

NOTE: it is acceptable to group multiple strains/lines on a single row AS LONG AS the description of potential adverse phenotypes is the same for all strains/lines included in that row. For example, you may be using a number of transgenic lines. You are not required to list every line as long as the expected phenotypes are the same.

General Information	Strain Origin	Decription of Strain and Adverse Phenotypes (if any)
Strain or Lab Name Porcine (domestic) Is strain irreplaceable? ○ Yes ◉ No	◉ Commercial Vendor ○ Import from Colleague ○ Existing colonies bred at UofL ○ New genetically-modified line created at UofL ○ Wild Caught	Describe any adverse phenotypes (diabetes, tumor growth, seizures etc.) Animals are expected to develop healthy abdominal cavity. The animals will be monitored carefully post treatment and euthanatized.

8.4 Are any of the strains/lines above genetically-modified (transgenic, knock-out, knock-in, etc.)?

○ Yes ◉ No

8.7 Are you willing to share tissues from animals or transfer live animals to other colleagues at U o f L?

◉ Yes ○ No

8.8 Related Proposals

Are the experiments similar or related to those described in another proposal for a different species? For example, multiple species may be needed to satisfy regulatory requirements.

○ Yes ◉ No

9.0 Lay Project Summary (250 words max)

9.1 Provide a non-technical summary of the proposed research, using language that a person not trained in biomedical sciences can understand. Describe the significance of the project and the reasons for which it has been proposed. This description should allow the reader to weigh the potential human or other animal health benefits against animal welfare concerns.

Lay Summary (250 words maximum):

Over the past two decades, minimally invasive surgery has grown in popularity. The introduction of larger cameras and instrumentation has caused the need for an increase in trocar sizes. These trocars

leave open incisions in the abdominal wall, which can lead to hernias and bowel obstructions requiring further surgery. An increasingly obese society brings about an increase in the number of minimally invasive abdominal surgeries required for a population at the highest risk for hernia formation. It is recommended that trocar sites of 10 mm or more be closed. Additionally, all trocar sites should be closed in pediatric patients.

Following laparoscopic surgery, there is a need in many cases to close the trocar sites to prevent hernias. There are existing devices to close the fascial layer,but using them can be difficult and time consuming. There does not appear to be a need to actually stitch the fascial layer, as the existing devices do, but rather simply blocking the fascial layer so it is closed off appears to be enough to prevent hernia formation. The device will be inserted through the trocar wound site, deployed and attached to the fascial layer and finally cinched tight to ensure a secure attachment. The device will be comprised of a bioabsorbable material such as PLA (polylactic acid) similar to existing polymer based bioabsorbable sutures in the market.

This is a pilot study to demonstrate device efficacy, ease of deployment/use and functionality within living tissue.

10.0 Technical Summary (800 words max)

10.1 Technical Summary

Describe specific aim(s) and the long-term goals of the project.

Over the past two decades, minimally invasive surgery has grown in popularity. The introduction of larger cameras and instrumentation has caused the need for an increase in trocar sizes. These trocars leave open incisions in the abdominal wall, which can lead to hernias and bowel obstructions requiring further surgery. An increasingly obese society brings about an increase in the number of minimally invasive abdominal surgeries required for a population at the highest risk for hernia formation. It is recommended that trocar sites of 10 mm or more be closed. Additionally, all trocar sites should be closed in pediatric patients.

Following laparoscopic surgery, there is a need in many cases to close the trocar sites to prevent hernias. There are existing devices to close the inner abdominal wall layer, but using them can be difficult, time consuming and a potential for localized pain for the patient. There does not appear to be a need to actually stitch the inner abdominal wall layer, as the existing devices do, but rather simply blocking the inner abdominal wall layer so it is closed off appears to be enough to prevent hernia formation. The device will be inserted through the trocar wound site, deployed and attached to the inner abdominal wall layer and finally cinched tight to ensure a secure attachment. The device will be comprised of a bioabsorbable material similar to existing polymer based bioabsorbable sutures in the market.

This is a pilot study to demonstrate device effectiveness, ease of placement and functionality within living tissue.

The success of this study will determine the potential of this device to be an alternative for surgeons to use in trocar site closure during laprooscopic surgery. The ability of this device to plug the paritoneal opening (created by trocar sites) and prevent herniation will determine the feasibility of this device.

11.0 Justification for Animal Use

11.1 Justification for Animal Use

Describe why the Proposal requires the use of animals, as opposed to *in vitro* or *in silico* approaches. (250 words or less)

Prior to safety and efficacy studies in human, pre-clinical animal studies are required. Ex-vivo experiments have been employed during the development of the technology to minimize the use of live animals in addition with studies performed in cadaver tissue. To replicate this procedure in tissues other than live abdominal tissue would not give the research team the desired material property for interaction between the developed wound closure device and the surrounding "slippery" abdominal tissue. The domestic pig model was chosen for further studies due to being the closest representation of human abdominal region in both size and weight. Animal studies in pigs will allow us to gauge the feasibility of applying the technology using routine laparoscopic procedures.

12.0 Assurance of Non-Duplication

12.1 Assurance of Non-Duplication

Provide a *written assurance* that the proposed activities do not unnecessarily duplicate previous or ongoing experiments. Describe methods and sources (journals, abstracts, *etc.*) to support this assurance. Include the date the search was performed, years included in the search, and keywords used. [Examples can be found in the help button to the right. Links to Databases: PubMed; Google Scholar]

Database Info	Keywords and Description of Results
PubMed 05/01/2018 Years Searched	List Keywords Laparoscopy, trocar wound closure, trocar site hernia, swine, animal model
All in database	Describe Results Insertion of trocars during a laparoscopic procedure is unavoidable. They are required for surgical procedural purposes. The database search shown in the table to the right with keyword combinations. Considering the size and weight of humans, the swine model is the only considerable option for animal studies. There were a few noted articles discussing the use of rabbit models for use in analogous studies for infant/pediatric laparoscopic procedures. There are noted articles that discuss the use of currently used medical devices for closure of trocar wound sites. Due to the novelty of the developed device, there were no published studies of trocar wound closure and herniation prevention that are similar.
Other - Please describe in results 05/01/2018 Years Searched	List Keywords Laparoscopy, trocar wound closure, trocar site hernia, swine, animal model
All in database	Describe Results From Science Direct Database Insertion of trocars during a laparoscopic procedure is unavoidable. They are required for surgical procedural purposes. The database search shown in the table to the right with keyword combinations. Considering the size and weight of humans, the swine model is the only considerable option for animal studies. There were a few noted articles discussing the use of rabbit models for use in analogous studies for infant/pediatric laparoscopic procedures. There are noted articles that discuss the use of currently used medical devices for closure of trocar wound sites. Due to the novelty of the developed device, there were no published studies of trocar wound closure and herniation prevention that are similar.

13.0 Experimental Groups

13.1 Describe Experimental Groups in Table Below

Provide a description of each experimental group in enough detail that reviewers can understand what happens to each animal assigned to that group.

-

Group Name or Number:

May be a user defined number or brief descriptive name. *Example*: heart transplant; dietary restriction.

-

Pain Class:

Class 0 - Animals will be acquired/held, but not used or manipulated in any way.

-

Class I - Animals will experience no pain or distress greater than that produced by routine injections or venipuncture and will not receive pain-relieving agents.

-

Class II - There is a potential for pain or distress which is minimized or eliminated by anesthetics, analgesics, and/or tranquilizers. Examples include induction of cancer/tumors, biopsy, endoscopy, vascular cut-down, footpad injections, use of adjuvants, implantation of chronic catheters, as well as survival and non-survival surgery.

-

Class III - Animals will experience pain or distress greater than that produced by routine injections or venipuncture and will not receive pain-relieving agents. Examples include exposure to agents or radiation levels that cause serious illness, research involving significant stress, or procedures involving prolonged restraint. A written justification (including supporting sources, journals, abstracts, etc.) for withholding pain-relieving agents must be provided in a following section.

-

Treatment/Description:

Devise a brief descriptive title for each procedure and describe the treatments each animal in this group will receive, including the time period between procedures. For studies in which the exact sequence or number of procedures cannot be determined, include a range of potential time periods and note the maximum potential procedures to be performed on the animals in that group. *Example:* This group will receive heart transplant followed by stem cell treatments. The stem cells will be given IV by tail vein injection 10 days after heart transplant surgery. In later sections you will describe "heart transplant" (Survival Surgery), "stem cell (IV) injection," etc. in the "*Procedures Table*" below.

Note: You may also include in each group a small number of variables as long as it is very clear from the description what will happen to the animals in these groups and the sample size used. Example: Following an acclimation period of 14 days, animals will receive treatment with XJ-47 in the drinking water at 3 levels (0, 15, and 30 mg/ml) for 30 days. At this point, we will perform intrasplenic implantation of WKW-95 (or control group) and follow groups of animals for an additional 30, 60, or 90 days until euthanasia and tissue collection. 10 animals/group x 3 dose groups x 2 implantation groups x 3 time points = 180.

-

Number of Animals in This Group:

The number of animals needed in the group is generally the sample size ("n"). If multiple variables were included in the "Treatment/Description," then this number may be a multiple of the sample size.

Group Name or Number and Pain Classification	Treatment/Description	Number of Animals in This Group
Group Name or Number Group 1 (7 Day) Pain Class (See definition above) Class II	60Kg domestic swine with healthy abdominal cavities will be anesthetized and 6 trocars will be inserted into the abdominal wall. Our novel closure device will be placed to close each of the trocar insertion sites. Buprenorphine SR (sustained release) will be administered subcutaneously for analgesia at the end of the surgical procedure so that it does not interfere with the analgesia provided by the anesthetic induction agents. This will provide analgesia for 48-72 hrs postoperatively. Meloxicam or carprofen will be	2

		administered intraoperatively for additional analgesia and will continue once daily for 48 hours post-op. Additional administration past 48 hrs will be based on pain assessment. A fentanyl transdermal patch may be applied to the animal over the neck immediately after surgery if it is found that buprenorphine and NSAID are insufficient for analgesia based on pain assessment and in consultation with RRF veterinary staff.The animals in Group 1 will be recovered for 7 days after surgery. Food and water will be provided for the animals as normally without special dietary conditions. At 7 days post device placement, the animals in Group 1 will be euthanized and evaluated for device implant healing progression at the wound sites. 2 animals in Group 1 = 2 animals total for Group 1.				
Group Name or Number Group 2 (14 Day) Pain Class (See definition above) Class II		60Kg domestic swine with healthy abdominal cavities will be anesthetized and 6 trocars will be inserted into the abdominal wall. Our novel closure device will be placed to close each of the trocar insertion sites. Buprenorphine SR (sustained release) will be administered subcutaneously for analgesia at the end of the surgical procedure so that it does not interfere with the analgesia provided by the anesthetic induction agents. This will provide analgesia for 48-72 hrs postoperatively. Meloxicam or carprofen will be administered intraoperatively for additional analgesia and will continue once daily for 48 hours post-op. Additional administration past 48 hrs will be based on pain assessment. A fentanyl transdermal patch may be applied to the animal over the neck immediately after surgery if it is found that buprenorphine and NSAID are insufficient for analgesia based on pain assessment and in consultation with RRF veterinary staff.The animals in Group 2 will be recovered for 14 days after surgery. Food and water will be provided for the animals as normally without special dietary conditions. At 14 days post device placement, the animals	2			

in Group 2 will be euthanized and evaluated for device implant healing progression at the wound sites. 2 animals in Group 2 = 2 animals total for Group 2.

13.2 Will You Maintain a Breeding Colony?

○ Yes ◉ No

13.4 Total Number of Animals Requested

Remember to include those from Breeding colony if relevant.

4

13.5 Animal Number Justification

Provide specific justification for the number of animals to be used <u>in each group</u> i.e., the sample size **. This must address statistical significance as it relates to experimental design. Please be as detailed as possible. Statistical power analysis or calculation given a known or expected error /failure rate and difference between groups is preferred, but experience with the model may be acceptable. [IACUC Fact Sheet] For teaching or training, the number of "students" per animal and expected number of training exercises may suffice.**
Note: Details of treatments, procedures, and other experimental variables should be included in the "Treatment/Description" column in the table above.

This is a pilot study to demonstrate device efficacy, ease of deployment/use and functionality. It is difficult to provide specific statistical justification for initial pilot studies, however the data collected from this pilot study will be used to statistically determine the animal numbers needed for further studies to move this device to human use in pre-clinical and clinical studies. From previous cadaver studies, statiscal analysis shows that a total of 12 replicates are neeed for each factor level for an 85% confidence.

14.0 Field Studies

14.1 Does proposal involve field studies?

○ Yes ◉ No

15.0 Procedures

15.1 Procedures Checklist

Indicate the types of procedures used in this proposal (check all that apply).

Definitions:

***Minor*:**

Any surgical intervention that does not expose a body cavity and causes little or no physical impairment. Example: laparoscopy; wound suturing; peripheral vessel cannulation; percutaneous biopsy; routine farm-animal procedures such as dehorning, castration; prolapse repair; and most procedures done on an "outpatient" basis in veterinary clinical practice.

Major:

Any surgical intervention that penetrates and exposes a body cavity; any procedure that has the potential for inducing permanent physical or physiologic impairment; and /or any procedure associated with orthopedics or extensive tissue dissection or transection.

-

For *Multiple* *Survival Surgical Procedures, i.e.,* surgical procedures that will be performed under separate anesthetic periods from which the animal will recover from each anesthetic period, describe each surgical procedure separately (there must be two separate procedures in the "Procedures Table").

-

Be sure to save often!

- ☐ None: Animals will be acquired/held and/or bred, but not used or manipulated in any way (exceptionally rare)
- ☐ Genotyping
- ☐ Individual Animal Identification
- ☐ Non-Surgical: may require anesthesia, but do not involve a surgical incision. Examples include test article administration, behavioral assessment, tissue collection (prior to euthanasia), imaging, irradiation, etc.
- ☐ Surgery - Non-Survival: a surgical procedure, performed under anesthesia, from which the animal does not recover from the anesthetic (also known as terminal or acute surgery)
- ☑ Surgery - Survival: a surgical intervention from which the animal is expected to recover from the anesthesia
- ☐ Surgery - Multiple: TWO or more survival surgical procedures (major or minor) between which the animal recovers from anesthesia

15.4 Procedures

Note when anesthetics or analgesics will be used, DO NOT provide dose, route, frequency, *etc.*, as these must be included in a later section.

Procedure Type and Name (descriptive title used in EXPERIMENTAL GROUP section above)	Description. Provide sufficient detail such that the reviewer can understand exactly what will occur and the potential impact of the procedure on the health and well-being of the animal. For surgical procedures include incision site, all tissue manipulations, temporary wound closures, etc. Indcate when anesthetics or analgesics will be used, but DO NOT include doses - these will be described in a later section.
Surgical - Survival Minor Procedure Name Survival placement of trocar placement of trocar closure device	Atropine, dexmedetomidine, ketamine, and butorphanol are mixed in the same syringe and are administered intramuscularly or in subcutaneous fat pad over the neck, behind the ear, at the time of anesthetic induction to provide sedation and induction of anesthesia for intubation. During surgery trocar incisions (12mm slits) will be made in the ventral abdomen of each animal (as previously performed in other studies for trocar testing in porcine models). A trocar will be inserted into one incision site at a time. Our novel closure device will be delivered into the fascia of the pig to plug the trocar incision wounds and close the trocar insertion sites. After performing this procedure for six trocar sites, the animals will be recovered from anesthesia. Meloxicam or carprofen will be administered intraoperatively for additional analgesia and will continue once daily for 48 hours post-op. Additional administration past 48 hrs will be based on pain assessment. A fentanyl transdermal patch may be applied to the animal over the neck immediately after surgery if it is found that

buprenorphine and NSAID are insufficient for analgesia based on pain assessment and in consultation with RRF veterinary staff.

Anesthesia, analgesia, post operation monitoring will be conducted by the RRF Vet. Staff.

Project Participants

Provide name(s) (in order of greatest involvement) of individual(s) participating in or involved with this *Proposal* (experimental procedures, animal observation or care, *etc.*) and describe their role in the proposed study. PI and Co-PIs should also be included. The experience described for each person should match their role in the studies described in this *Proposal*. If not, please indicate how they will obtain sufficient training.

Name	Role (List Specific Procedures to be performed)	Experience
Metzinger, Daniel S, M.D.	Will perform the laparoscopic procedure and deploy biodegradeable device in trocar wound site. Will be administering IM and SQ injections and Euthanasia.	See Online Training Log
Patel, Hares A	Will help design experiments and troubleshoot any of the mechanical functionality of the proposed device if adjustments need to be made once in vivo experiments begin.	See Online Training Log
Keynton, Robert S	Will be supervising and observing experiment.	See Online Training Log

If there are any non-UofL personnel who will be handling animals or performing any procedures as part of this Proposal, please provide their names, the functions they will perform, and the relevant experience /training they have in performing those functions.

Name	Procedures Performed and Experience
No records have been added	

☑ As Principal Investigator (or designee), I attest that the Key Study Personnel selected for this study have, or will obtain, the necessary experience, training, and are proficient, or will be proficient, in performing all of the procedures listed above.

16.0 Anesthetics, Analgesics, and Other Therapeutic Agents

16.1 List ALL pre-anesthetic, anesthetic, analgesic, tranquilizing agents, surgical support fluids, antibiotics, and other veterinary medical therapeutics to be used (even if their use has been described elsewhere in this *Proposal*). Examples include not only peri-operative drugs, but also such drugs as insulin for diabetic animals, or hot/cold packs.

Analgesics "PRN" or "as needed"

The USDA Research Facility Inspection Guide states that "PRN" or "as needed" frequency of administration is not acceptable unless there are detailed instructions and criteria for determining

administration of the drug. Non-pharmacological methods, such as hydrotherapy and hot/cold packs, should also be described. Availability of experienced personnel, especially at night and on weekends, should also be assured in protocol review.

IM = intramuscular, IP = intraperitoneal, IV = intravenous, PO = per os (by mouth), SC = subcutanous

Be sure to save often!

Click "Save and Continue" button at top right of screen. (You will move to the next section. You can return to "Anesthetics, Analgesics, and Other Therapeutics" by clicking the appropriate section on the left. This annoying feature will be fixed in future releases!)

Name and Purpose (check labels)	Dose (mg/kg) and Route (check labels).	Frequency (e.g., twice daily) and Duration (e.g., once, three weeks) - check labels
Name: Atropine Purpose: Pre-anesthetic Other Use, Explain:	Dose: 0.025mg/kg Route: SC Other Route: or IM	Frequency: Provided at the time of anesthetic induction to provide sedation and induction of anesthesia for intubation. Duration: For the time the animal is sedated.
Name: Isoflurane Purpose: Anesthetic Other Use, Explain:	Dose: 1-5% Route: Inhalation Other Route:	Frequency: initially given via nose cone to produce light anesthesia if injectable anesthesia is insufficient for intubation and then given via the endotracheal tube for surgical anesthesia Duration: For the time before and during surgery.
Name: TKX Combination (Telazol, Ketamine, Xylazine) Purpose: Anesthetic Other Use, Explain: (induction)	Dose: 0.025ml of cocktail per kg body weight Route: IM Other Route: or SC	Frequency: Provided at the time of anesthetic induction to provide sedation and induction of anesthesia for intubation. Duration: For the time the animal is sedated.
Name: Buprenorphine SR Purpose: Analgesic Other Use, Explain:	Dose: 0.3 mg/kg Route: SC Other Route:	Frequency: administered subcutaneously for analgesia at the end of the surgical procedure so that it does not interfere with the analgesia provided by the anesthetic induction agents. This will provide analgesia for 48-72 hrs postoperatively. Duration:

48-72 hours postoperatively.

Name	Dose	Frequency
Meloxicam	0.2 mg/kg	administered intra-operatively for additional analgesia and will continue once daily for 48 hours post-op. Additional administration past 48 hrs will be based on pain assessment.
Purpose	Route	
Analgesic	IV	
Other Use, Explain	Other Route:	Duration
	or SC or PO	Continue once daily for 48 hours post-op. Additional administration past 48 hrs will be based on pain assessment.

Name	Dose	Frequency
Fentanyl	5 up/kg/hr	may be applied to the animal over the neck immediately after surgery if it is found that buprenorphine and NSAID are insufficient for analgesia based on pain assessment and in consultation with RRF veterinary staff
Purpose	Route	
Analgesic	Other	
Other Use, Explain	Other Route:	Duration
	Transdermal patch	Post-operatively administered based on pain assessment and in consultation with RRF veterinary staff.

Name	Dose	Frequency
Carprofen	2-4 mg/kg	administered intraoperatively for additional analgesia and will continue once daily for 48 hours post-op. Additional administration past 48 hrs will be based on pain assessment.
Purpose	Route	
Analgesic	IV	
Other Use, Explain	Other Route:	Duration
	or SC or PO	Continue once daily for 48 hours post-op. Additional administration past 48 hrs will be based on pain assessment.

Name	Dose	Frequency
Dexmedetomidine	0.02 mg/kg	Provided at the time of anesthetic induction to provide sedation and induction of anesthesia for intubation.
Purpose	Route	
Anesthetic	SC	
Other Use, Explain	Other Route:	Duration
	or IM	For the time the animal is sedated.

Name	Dose	Frequency
Ketamine	5 mg/kg	Provided at the time of anesthetic induction to
Purpose	Route	

Anesthetic	SC	provide sedation and induction of anesthesia for intubation.
Other Use, Explain	Other Route:	Duration
	or IM	For the time the animal is sedated.
Name	Dose	Frequency
Butorphanol	1 mg/kg	Provided at the time of anesthetic induction to provide sedation and induction of anesthesia for intubation.
Purpose	Route	
Anesthetic	SC	
Other Use, Explain	Other Route:	Duration
	or IM	For the time the animal is sedated.
Name	Dose	Frequency
Antisedan	0.24mg/kg	If the animal is slow to recover from anesthesia, antisedan may be administered to reverse the dexmedetomidine and partially reverse the ketamine.
Purpose	Route	
Other (describe in box below)	IM	
Other Use, Explain	Other Route:	Duration
Anesthetic reversal		Post-operatively administered based on pain assessment and in consultation with RRF veterinary staff.
Name	Dose	Frequency
LRS or Normosol-R	10 ml/kg/hr	An IV catheter will be placed in a marginal ear vein and LRS or Normosol-R will be administered for fluid support during surgery.
Purpose	Route	
Other (describe in box below)	IV	
Other Use, Explain	Other Route:	Duration
Fluid support		During surgery.
Name	Dose	Frequency
Cefazolin	20 mg/kg	just prior to surgery and will receive oral cephalexin BID for 7 days post-operatively to prevent infection since these animals may lay on their incisions in the pens.
Purpose	Route	
Antibiotic	IV	
Other Use, Explain	Other Route:	Duration
		7 days post-operatively
Name	Dose	Frequency
KCL	75-150 mg/kg	At the time of Euthanasia
Purpose	Route	Duration
Other (describe in box below)	IV	For the time of Euthanasia

Other Use, Explain	Other Route:
Euthanasia	

In the text box below, provide additional information on the use of the agents listed above. Examples may include use of certain analgesics pre-emptively, clarifying different anesthetic regimens for specific procedures, anesthetics used in combination, decision making process used to determine frequency or duration, etc.

For survival Surgical Procedures (frequency and duration):
a. Atropine, dexmedetomidine, ketamine (5 mg/kg), and butorphanol are mixed in the same syringe and are administered intramuscularly or in subcutaneous fat pad over the neck, behind the ear, at the time of anesthetic induction to provide sedation and induction of anesthesia for intubation.
b. Isoflurane: initially given via nose cone to produce light anesthesia if injectable anesthesia is insufficient for intubation and then given via the endotracheal tube for surgical anesthesia.
c. An IV catheter will be placed in a marginal ear vein and LRS or Normosol-R will be administered for fluid support.
d. Animals may be placed on mechanical ventilation if they are not ventilating well enough on their own.
e. Buprenorphine SR (sustained release) will be administered subcutaneously for analgesia at the end of the surgical procedure so that it does not interfere with the analgesia provided by the anesthetic induction agents. This will provide analgesia for 48-72 hrs postoperatively.
f. Meloxicam or carprofen will be administered intraoperatively for additional analgesia and will continue once daily for 48 hours post-op. Additional administration past 48 hrs will be based on pain assessment (see post-operative observations attachment).
g. A fentanyl transdermal patch may be applied to the animal over the neck immediately after surgery if it is found that buprenorphine and NSAID are insufficient for analgesia based on pain assessment and in consultation with RRF veterinary staff.
h. If the animal is slow to recover from anesthesia, antisedan may be administered to reverse the dexmedetomidine and partially reverse the ketamine.
i. Animals will receive cefazolin IV just prior to surgery and will receive oral cephalexin BID for 7 days post operatively to prevent infection since these animals may lay on their incisions in the pens.

Notes:
Telazol® must be stored refrigerated once reconstituted.
To mix: reconstitute Telazol® with large animal Xylazine (5 ml of 100mg/ml) instead of water; add 5 ml ketamine (concentration of 100mg/ml)

17.0 Anesthesia and Anesthetic Monitoring

17.1 Will animals be anesthetized for any reason OTHER THAN Euthanasia?

(•) Yes ( ) No

17.2 Animal Preparation for Anesthesia

Select those that apply

- [x] Observation for normal behavior
- [ ] Pre-anesthetic diagnostics (e.g., hematology, serum blood chemistry panel)
- [x] Overnight fasting (NON-RODENT MAMMALS ONLY).
- [x] Use of sedatives (describe in Anesthetics, Analgesics, and Other Therapeutics table).
- [ ] Placement of non-medicated ophthalmic ointment in eyes.
- [ ] Other (describe below):

17.3 Monitoring Anesthetic Depth

Select those that apply

- [x] Body temperature measurement and support using temperature-measuring probe.
- [x] Use of intra-procedural fluids (describe in Anesthetics, Analgesics, and Other Therapeutics table).
- [x] Anesthetic depth checked at intervals no less than 15 minutes (describe other intervals below).

☐ Anesthetic depth verified by withdrawal reflex (toe/tail pinch).
☐ Other methods of anesthetic monitoring and animal support during anesthesia and/or surgery:

Provide additional information if needed.

Heart rate, respiratory rate, SpO2, blood pressure, body temperature, and reflexes will be monitored throughout the anesthetic period and will be recorded on a log at least every 10 minutes by a dedicated anesthetist. Depth of anesthesia will be monitored by the anesthetist. If the vital signs increase or decrease the anesthesia will be adjusted accordingly.

During recovery the animals will be monitored continuously until they are able to breathe spontaneously and will either be kept on a ventilator or ventilated manually with an Ambu bag until they are breathing spontaneously.

18.0 Surgical Preparation and Support

18.1 Will animals undergo surgical procedures?

◉ Yes ○ No

18.2 Animal Preparation

☑ Removal of hair from the incision site with clippers (describe use of razors or depilatories in the space below).
☑ Preparation of surgical site with chlorhexidine or providone-iodine followed by a rinse with sterile water, saline, or alcohol; repeated at least 3 times.
☐ Other animal preparation procedures not describe above or in the "Anesthesia and Anesthetic Monitoring" section.

Surgical staff will wear sterile gowns, caps, masks, sterile gloves, and shoe covers. The animals will be anesthetized, prepped with a standard surgical prep after hair removal with clippers in the surgical preparation area. Animals will be transported to an RRF OR.

18.3 Aseptic Surgical Technique

Select those that apply
***Note*: survival surgery on ALL species must be performed using aseptic procedures. Surgical procedures on non-rodent mammals must be conducted in RRF-managed facilities intended for that purpose. [IACUC Policy]**

☑ Sterilize instruments via autoclave and/or ethylene oxide.
☑ Sterilize instruments via chemical (cold) sterilization (describe below).
☑ Use of separate instruments between serial surgeries.
☑ Sterilization of instrument tips between surgeries using hot bead sterilizer.
☐ Sterilization of instrument tips between surgeries using chemical (cold) sterilants (describe below).
☑ Use of sterile gloves.
☐ Use of tips-only technique.
☑ Use of sterile drapes.
☐ At least two-layer closure, using absorbable material to close muscle fascia and/or subcutaneous tissue.
☐ Use of monofilament non-absorbable suture material or surgical staples (wound clips) for the skin incision.
☐ Other (describe below):

Outline additional/alternative methods used (e.g., for non-survival surgery) or for maintaining asepsis.

Surgical staff will wear sterile gowns, caps, masks, sterile gloves, and shoe covers. The animals will be anesthetized, prepped with a standard surgical prep after hair removal with clippers in the surgical preparation area. Animals will be transported to an RRF OR.

18.4 Post Procedural Monitoring and Care

Select all that apply

- [ ] Not applicable, animals will not recover from anesthesia
- [x] Constant monitoring of animals until fully ambulatory.
- [x] Complete surgical records, including anesthetic monitoring.
- [ ] Mark cage cards with date of surgery (rodents).
- [x] Daily observation at least 7-14 days.
- [ ] Skin incision closure (sutures or wound clips) removal at 7-14 days (otherwise describe below).
- [x] Continue and record post-operative care, including use of analgesics and daily observations.
- [x] Use of postoperative fluids, antibiotics, or other therapeutics (described in Anesthetics, Analgesics, and Other Therapeutics table).
- [x] Analgesics (described in Anesthetics, Analgesics, and Other Therapeutics table) will be provided for at least 48 hours. Criteria used to determine that additional analgesic use beyond 48 hours is described below.
- [ ] Non-pharmacological analgesia (e.g., cold packs, water baths) will be used (describe below).
- [ ] No analgesics will be used (provide justification for withholding analgesia below).
- [ ] Other (describe below):

Additional Post-Surgical Care.

Briefly describe additional post-procedural care in the space below. DO NOT list specific drug doses; they should be provided in the Anesthetics, Analgesics, and Other Therapeutics table.

- Animals will be monitored continuously by RRF veterinary staff during anesthesia recovery until they are ambulatory and exhibiting species specific behavior. Animals will be evaluated daily by RRF veterinary staff for activity level, incision appearance, eating, drinking for at least 7 days post-surgery and then weekly. If any animal is experiencing problems, then it will be monitored daily until the problem is resolved.
- A post-surgery pain assessment chart will be utilized.

18.5 Required Clinical Records

- [ ] Not Applicable: Protocol does not involve surgery.
- [x] Individual animal health records will contain documentation of peri-operative surgical support, surgical procedures performed, anesthetic monitoring, post-operative monitoring and support (required for non-rodent mammalian species).
- [x] Template peri-operative surgical records provided by RRF veterinary personnel will be used.
- [x] Laboratory records will contain documentation of peri-operative surgical support, surgical procedures performed, anesthetic monitoring, post-operative monitoring and support.
- [ ] Other (describe below):

19.0 Privately-Owned Animals

19.1 Privately-Owned Animals

Does this Proposal include the use of any privately-owned animals?

( ) Yes (•) No

20.0 Non-Standard Housing, Food and Water (or Other Special Considerations)

20.1 Indicate which of the following, if any, pertain to this proposal

- ☐ Animals require special housing conditions (e.g., individual housing, special caging).
- ☐ Animals receive special food
- ☐ Animals receive special drinking water
- ☐ Animals will experience food or drinking water restriction or regulation
- ☐ Use of non-sterile or expired medical materials (disposable surgical supplies)
- ☐ Animals will be physically restrained for prolonged periods of time. Brief manual restraint for the purpose of performing routine clinical or experimental procedures (< 15 minutes for rodents, <30 minutes other mammals) need not be described unless the procedures will cause pain or distress.

21.0 Collaborating Institutions

21.1 Does this project involve the use of animals at any other institution?
***Example:* We perform a surgery at U of L and a colleague at another instution performs a very specialized procedure.**
Note: This does not include collaborations in which you import a new strain from a collaborator.

See **IACUC Policy**

○ Yes ◉ No

22.0 Biological Agents

22.1 Indicate which Types of Biological Agents that will be administerd to animals.
-
***Examples: Mammalian cell lines; bacteria; other microbes; viruses; materials of human or non-human primate origin (e.g. antibodies etc.); toxins of biological origin (e.g., Complete Freund's Adjuvant, pertussis toxin).* These tables will be reviewed by the Biological Safety Office to determine the need for IBC Registration and/or applicable SASPs.**
-
Select ALL that Apply

- ☑ Not Applicable: No Biological materials will be used in live animals
- ☐ Microbial Agents or Parasites (bacteria, viruses, protozoa, etc.)
- ☐ Cells or Tissues (cell lines, primary tisues or cells, etc.)
- ☐ Other Biological Material (antibodies, rDNA, toxins of biological origin such as Complete Freund's Adjuvant, pertussis toxin, etc.)

23.0 Chemical Agents

23.1 Will animals be exposed *in vivo* to ANY other chemical agent not included in the "Anesthetics, Analgesics, and Other Therapeutic Agents" table above? This includes investigational drugs, test articles, or any other chemical agent introduced into the animal other than biological or radiological materials.

○ Yes ◉ No

24.0 Radiation or Other Physical Hazards

24.1 Will animals be exposed to radiation (e.g., isotopes, lasers, irradiators) or other physical hazards (e. g., loud noises)?

- ☐ Radioactive Material
- ☐ Cs-137 irradiator

- [ ] X-Ray radiation
- [ ] Other (magnet, lasers, noise, etc.)

25.0 Agent Administration and Return to RRF

25.1 Will live animals be returned to the RRF after exposure to hazardous substances (biological, chemical, or radioactive)?

- [x] Not Applicable. No hazardous agents used or animals are not returned to the RRF
- [ ] Biological Exposure then return to RRF
- [ ] Chemical Exposure then return to RRF
- [ ] Radioactive Material Exposure then return to RRF

26.0 Euthanasia or Other Disposition

26.7 Please select all methods of euthanasia that will be employed in this proposal. - Non Rodent Mammal

- [x] Barbiturate injection (IV), overdose to effect. Death will be ensured by careful physical examination and an adjunctive physical method such as bilateral thoracotomy or exsanguination / vital organ (brain, heart, lungs, liver, or kidneys) removal.
- [ ] General anesthesia as described in "Anesthetics, Analgesics, and Other Therapeutics," followed by an adjunctive physical method such as bilateral thoracotomy, exsanguination or vital organ (brain, heart, lungs, liver, or kidneys) removal, decapitation, or perfusion.
- [x] General anesthesia as described in "Anesthetics, Analgesics, and Other Therapeutics," followed by intravenous or intracardial injection of potassium chloride (KCl, at least 75-150 mg/kg).

26.8 If methods of euthanasia other than those listed above will be employed, please describe their use in detail.

26.9 For animals that will not undergo euthanasia at the end of these studies, provide a description of their final disposition. If this includes assignment to another *Proposal*, identify the other *Proposal* (if known) and estimate the minimum time period before using the animal(s) in subsequent procedures.

27.0 Non-Pharmaceutical-Grade Agents

27.1 Are ANY of the agents, substances, drugs, test articles, etc. to be used in live animals chemical grade, that is, not pharmaceutical grade?

- ( ) Yes
- (•) No

28.0 Non RRF Study Site(s)

28.1 Will animals be transported to and used in rooms outside of the RRF?

- ( ) Yes
- (•) No

29.0 Consideration of Alternatives

29.1 Indicate HIGHEST Pain Classification of Procedures in this protocol.

- ○ Class 0 - Animals will be acquired/held, but not used or manipulated in any way.
- ○ Class I - Studies in which animals will experience no pain or distress greater than that produced by routine injections or venipuncture and will therefore receive no pain-relieving agents.
- ◉ Class II - Studies in which there is a potential for pain or distress which is minimized or eliminated by anesthetics, analgesics, and/or tranquilizers. Examples include biopsy, endoscopy, vascular cut-down, footpad injections, use of adjuvants, implantation of chronic catheters, as well as survival and non-survival surgery.
- ○ Class III - Studies in which animals will experience pain or distress greater than that produced by routine injections or venipuncture and will not receive pain-relieving agents. Examples include exposure to agents or radiation levels that cause serious illness, research involving significant stress, or procedures involving prolonged restraint. A written justification (including supporting sources, journals, abstracts, etc.) for withholding pain-relieving agents must be provided in a following section.

29.2 List of Procedures

List all procedures potentially associated with more than minor pain or distress (*e.g.*, nephrectomy, craniotomy, forced exercise, use of Complete Freund's Adjuvant). This is meant to help you identify keywords needed in literature database searches for alternatives to the potentially painful or distressful procedures.

Laparoscopy, Trocar Incisions and Device Placement

29.3 Consideration of Alternatives

Provide a written description of the methods (*e.g.*, literature database search) and sources (*e.g.*, databases, review articles, scientific meetings) used to determine that alternatives to painful procedures were not available. *Note*: Unless a compelling justification can be made without it, support your assurance by conducting a literature database search.

-

Note: the USDA Research Inspection Guide states that teaching exercises involving potential pain and distress (e.g., non-survival surgery) using animals should also consider alternatives such as veterinary mannequins, live tissue alternatives, and mechanical teaching devices. Protocols involving toxicity studies should also consider alternatives such as local lymph node assay, up-and-down procedures (see http://iccvam.niehs.nih.gov/about/overview/htm).

A literature database search was performed to seek alternatives to performing this basic laparoscopic surgerical process in swine. Numerous databases were searched for alternatives to painful procedures, alternatives to safety data collection for support of submission to the FDA and to assure that the best practices are being performed in swine regarding analgesia, anesthesia, monitoring, etc. Database searches and discussions with the RRF Veterinarian were also performed to ensure that the animals are receiving the best anesthesia, analgesia and are monitored properly for abdominal surgeries.

We did not find any articles offering alternatives to the proposed laparoscopic procedure using swine. During our searches we did identify one recent article that may be of interest to you in that it discusses methods for closing laparoscopic trocar sites larger than 10 mm. Shown below.

Van Sickle KR[1], **Development of an animal model to investigate optimal laparoscopic trocar site fascial closure**, **J Surg Res.** 2013 Sep;184(1):126-31

USDA Policy stipulates that for each search performed, you must provide the information requested in the table below. For additional information regarding performing such searches, see the **IACUC Information Sheet**. A representative in the Kornhauser Library is also available to assist you: **j0chen05@exchange.louisville.edu**
Keywords must include the procedure itself (*e.g.*, abdominal surgery, nephrectomy, thoracotomy, craniotomy, etc. Keywords should include terms for refinement as well as replacement for the painful procedure, such as analges*, anesthe* or anaesthe*, advers*, monitor*, pain*, distress*, stress*, welfare.

Database Name / Search Date	Keywords Used / Results
Database Name	

PubMed

Date Search Performed

06/19/2018

Dates seached, if not ALL

List keywords (searches should be performed for alternatives to each of the potentially painful procedures listed in subsection 3 above).

Laparoscopy + Swine + Analges, Laparoscopy + Swine + Anesthe, Laparoscopy + Swine + Advers, Laparoscopy + Swine + Monitor, Laparoscopy + Swine + Pain, Laparoscopy + Swine + Distress, Laparoscopy + Swine + Stress, Laparoscopy + Swine + "Trocar Wound Closure" + Analges, Laparoscopy + Swine + "Trocar Wound Closure" + Anesthe, Laparoscopy + Swine + "Trocar Wound Closure" + Advers, Laparoscopy + Swine + "Trocar Wound Closure" + Monitor, Laparoscopy + Swine + "Trocar Wound Closure" + Pain, Laparoscopy + Swine + "Trocar Wound Closure" + Distress, Laparoscopy + Swine + "Trocar Wound Closure" + Stress

Results:

At this time there are no alternatives to painful procedures such as abdominal laparoscopy when performing pre-clinical work for devices and treatments that are being submitted to the FDA for approval to demonstrate safety prior to the use of those devices in humans. In addition, there are no alternatives to using live, bleeding and "slippery" tissue to evaluate the interaction of our novel trocar site wound closure device in living tissue. The analgesia, anesthesia and animal welfare described in this protocol follow procedures to decrease pain and follow the best practices described in numerous manuscripts.

Database Name

Other - Please describe in results

Date Search Performed

07/20/2018

Dates seached, if not ALL

List keywords (searches should be performed for alternatives to each of the potentially painful procedures listed in subsection 3 above).

Laparoscopy, trocar wound closure, swine, analges*, anaesthe*, advers*, monitor*, pain*, distress*, stress*

Results:

-From database: Science Direct-
At this time there are no alternatives to painful procedures such as abdominal laparoscopy when performing pre-clinical work for devices and treatments that are being submitted to the FDA for approval to demonstrate safety prior to the use of those devices in humans. In addition, there are no alternatives to using live, bleeding and "slippery" tissue to evaluate the interaction of our novel trocar site wound closure device in living tissue. The analgesia, anesthesia and animal welfare described in this protocol follow procedures to decrease pain and follow the best practices described in numerous manuscripts.

29.5 Humane Endpoints

For some Class I and *all* Class II and III procedures, there is a potential for adverse effects. Humane endpoints are objective signs indicating a pain/distress level that warrants intervention

(usually euthanasia), regardless of experimental timelines. These may be specific for each procedure or may be general for an experimental group or the entire *Proposal*. Often, basic "sick animal" signs such as inappetance or lethargy lasting over 24-48 hours or weight loss exceeding 10% are used. Other signs/criteria may be more appropriate for this study. [IACUC Policy and Pain Scoring Sheet Templates]

-

Make sure that your response

1. **Precisely defines the humane endpoint, including assessment criteria**
2. **Describes the frequency of animal observation**
3. **Describes the response required upon reaching the humane endpoint**

Experimental Group or Procedure	Endpoint and Assessment Criteria	Frequency of Observation	Response
Survival placement of trocar closure device	Device Dislodges and Non-Obstructive Herniation Occurs	Monitor and Evaluation by RRF Staff	Euthanize
Survival placement of trocar closure device	Wound infections	Monitor and Evaluation by RRF Staff	Treat with antibiotics
Survival placement of trocar closure device	Weight loss > 10% of baseline body weight animals	Monitor and Evaluation by RRF Staff	Euthanize
Survival placement of trocar closure device	Any unforeseen complications, or if the animals are not active, eating, or drinking	Monitor and Evaluation by RRF Staff	The animals will be evaluated by an RRF veterinarian and their recommendations will be followed.

30.0 Other Information for IACUC Review

30.1 Is there any additional information that may assist the IACUC in their review, *e.g.*, request for exemptions to IACUC policies not described elsewhere in this Proposal?

○ Yes ◉ No

31.0 End of Form

31.1

STOP

To Submit Proposal click "Save & Continue," and complete the Initial Review Submission Packet Otherwise - Log Out or return to the sections you wish to revise.