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December 9, 2016

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Dear Dr. Lee,

Attached is our Final Design Report. The purpose of this document is to convey what our design project is, why it is needed, and who it will benefit. This report also contains the different design ideas we have had, the design that we proceeded with, and for what reasons it was selected. Finally, this document includes all of the testing performed on our prototype for our proof-of-concept. We will also details the future steps that would need to be taken to further test our product and the work that would need to be done in order to patent this product for use.

If you have any questions or concerns with the content of this document, please feel free to email our Communications Officer, Sara Parker, at sparke26@vols.utk.edu

We would like to thank you for all of your help this year and we look forward to working with you in the future.

Sincerely,

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FINAL DESIGN REPORT FOR THE GASTROINTESTINAL ANASTOMOSIS DEVICE AND LAWRENCE LEE, MD, UNIVERSITY HEART SURGEONS

May 7, 2017

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EXECUTIVE SUMMARY

The proposed device design is intended to streamline anastomosis procedures while improving efficacy and duration of the newly formed connection. The device will consist of a conduit upon which two intestinal canals may be mounted and a male-and-female clamp which will fix the intestines onto the device. The clamp will be used to further secure the mechanical fixation of our device and to provide external support as another layer of defense against failure. Our device design will facilitate material flow on the interior of the device and the union of two mounted tissue segments on the exterior surface. The material that is selected for our final design is 85:15 PLGA, which is biocompatible and will degrade in 5-6 months.

This design will allow for a reliable mechanical fixation supported by an additional chemical fixation by way of the tissue adhesive, BioGlue. This double fixation will ensure the integrity of the graft-tissue attachment. Additionally, the BioGlue is intended to stimulate the growth of the two tissue segments until union. This should ensure the longevity of the anastomosis. Avoidance of occlusion events, a facet of many anastomotic devices that is short-lived, should be achieved by the biodegradable nature of the main conduit. This will allow for internal disposal of the device without the need of additional intervention. Once the device is disposed, all that remains will be the newly formed, continuous tissue connection. The clamp is designed as a hinge, so that it can be easily applied around the tissues without causing further damage. This directly relates to necrosis avoidance by the graft and target tissues. These aspects will ensure the reliability of the graft-to-target connection, the longevity of the union, the avoidance of occlusion events, and the survival of the involved tissues per stakeholder requirements.

As anastomosis procedures are performed for tubular tissue connections, a device or device system that streamlines the anastomotic process, reduces occlusion risk, and ensures connection efficacy would find application within many anastomotic procedures. This is a relatively large market to be explored as current devices are only applicable to tissue specific anastomotic procedures and come with many of the previously mentioned pitfalls. Our design may be applicable to many anastomotic procedures after material composition adjustments that would account for varied body environments. The base conduit connection design would remain consistent throughout the tissue specific iterations. This would allow for a standardization of anastomotic procedures and reduce the training required to master such a technique.

The prototype meets and surpasses all of the requirements of the manufacturing specifications. The prototype has been manufactured in the manner that was described and by ProtoLabs, the company that was selected. This prototype exceeds the requirements because the clamp has been modified to include a hinge to make the application of the hinge less damaging to the tissue. The prototype has been manufactured under budget, the time that it takes to complete implement is very quick (roughly 3 minutes), and it has a lower failure rate than staples/hand suturing in our testing. Testing of our device included tensile tests with and without the conduit, and leakage tests. Our final device will be biocompatible and sterilizable. This prototype fulfills all of our design needs provided by our stakeholder. These needs include efficacy, ease of use, biocompatibility, easy on tissue, adjustable/applicable to varying tissue sizes, and it will be degradable.

BACKGROUND

An anastomosis is any surgical connection between two tubular structures such as blood vessels or intestines. Currently, anastomosis procedures are performed by hand-suturing or stapling the ends of the vessels together. While the more recent development of gastric staplers has made the anastomosis process easier, most of the associated risks remain.¹ There are many complications associated with both of these methods, including bleeding, leakage, and stricture.¹ In fact, most studies have not found a significant difference between suturing and stapling with respect to the associated risks.¹⁻⁶ For gastrointestinal anastomosis, anastomotic leakage is a major complication. Depending on the region in which re-sectioning is performed, leakage rates range anywhere between 0.5-20%.⁷⁻¹² Further, the morbidity rate following leakage has been shown to range from 20%-30% and the mortality rate ranges from 7% to 14% (compared to an overall mortality of about 4%).^{7,8,13-16} In addition to leakage, stricture is a major complication of anastomosis procedures, specifically those that involve stapling. Stricture after staple procedures are estimated to occur in approximately 3 to 30% of all colorectal anastomoses; further, about 28% of these cases require an additional procedure.¹⁷ It is important to note that the wide ranges of complications in anastomosis procedures is attributed to patient variation and discrepancies among surgeons.^{8,17} Compounding the effect of the occurrence of adverse events, gastrointestinal anastomosis procedures need to be performed for a variety of reasons including gastric bypass procedures, colorectal cancer (the second most common type of cancer), bacterial infections or gangrene, ulcerative colitis, Irritable Bowel Disease, and Crohn's Disease. Thus, because of the frequency at which anastomosis procedures are performed and the severe risk incurred when the connection fails, it is imperative that efficacious, novel, and standardized solutions be explored. A comprehensive list of relevant patents and devices can be found in **APPENDIX A**.

With respect to a new device for anastomosis procedures, there are a number of needs presented by the project stakeholder. Most importantly the device must be effective by providing a stable connection between two vessels without leaking or blocking. A device that is not as effective as the current method would be a waste of time and money. The next essential need for this device is the ease of use. Most surgeons will not want to use or be trained with a product that is not easy to use. An additional need is biocompatibility. When a foreign material is used during the procedure or left in the body, the material must not elicit a foreign body response. Additionally, the device must be compatible with various intestine sizes. Finally, the device must not be too hard on the tissue, causing additional damage. Following the "needs", other crucial factors when creating an anastomosis device are the "wants". These features are desirable, but not completely necessary for the device's success. The primary want expressed to us by the project stakeholder (Dr. Lee) is a sutureless method for anastomosis procedures. This could prevent excessive damage to the underlying tissue, thereby, decreasing the inflammatory response and chance of stricture. Another important "want" that was expressed is comfortability. If the device is not comfortable to use, it would be difficult to convince surgeons that our device is superior to other methods. The final "want" is for the device to be low cost. This is considered a "want" because the device may be more effective than hand-suturing, while being more expensive to produce.

A viable design solution that improves on current anastomosis methods has many health implications. Decreasing the time it takes for surgeons to perform the procedure will minimize the time needed for the patient to be under anesthesia. Additionally, if a device or material could be used to create

the anastomosis instead of hand suturing, the procedure method could be better standardized across all surgeons. This would limit the subjectivity and human error associated with this procedure, and ultimately improve the success rate. In addition, a more standardized procedure would create a system where failures can be clearly documented and it will be easy to identify device shortcomings and human error, allowing the designers to create a better device in the future. The main people that would benefit from this device are gastrointestinal surgeons, because the surgery would be easier to perform and execute correctly. All patients that must undergo a procedure of this nature would benefit from this, as well because success rates would improve.

PROBLEM DEFINITION

The goal of the project is to design a device that will make the anastomosis procedure *easier*, improve overall *success rates* by limiting blockages and leakages, and *standardize* anastomosis procedures. Our key business objectives are productivity, marketing, and competitive analysis. By grounding our project in these objectives, we will produce a high-quality design that can be marketed and outcompete competitor products.

Based on the aforementioned needs, the following table is a list of functions and requirements that the device must satisfy to be considered successful and how success will be measured for each of these requirements (**Table 1**). Here, efficacy refers to the device's ability to form a stable connection without leaking. This required function will be measured by analyzing the leakage rates of fluids with varying viscosity through the site of connection. The needs will be satisfied if the solution is efficacious and there is no leakage at the anastomosis site. Another major function of the design is ease of use. Users must be able to use the device easily, without complication and extensive training. To ensure that this function is satisfied, the time of application will be measured and compared to the expected ~3 minute time of conventional suture and staple-based methods. Further, a standardized procedure and result should be established to ensure that human error is not a factor. The standardization function will be measured by observing the efficacy and ease of use function across multiple users. Lastly, biocompatibility of the solution (and the ability of the product to biodegrade) is a requirement that must be satisfied. This will be ensured by analyzing and reviewing standards and specifications for biomedical devices and studying common biomaterials used for this application. This function is vital to the device's success because it is intended to be used in the body. Thus, an incompatible material will not be accepted.

Specific constraints as outlined by the project guidelines include time, cost, biocompatibility and efficacy. With only 6 months to refine, manufacture, and test the design, time is a major factor affecting design selection and refinement. In addition, the budget for the project is only \$3,000, so cost is a significant limitation that will need to be overcome. Because the device will require placing foreign materials into the body, the sterilization requirement is another constraint that may limit material selection. Each of the constraints may limit the materials and manufacturing processes that are available. Further, the device is expected to keep the anastomosis site open, without causing harm to the tissue.

Table 1. Function Breakdown Table. Listed are specific functions that correspond with stakeholder needs. The “Metric” column refers to the way that each of the listed functions will be measured to determine if the device is successful.

Function	Metric
Efficacy	Examine volume of leaked fluid during testing
Ease of Use	Comparison of procedure time to the expected time for current methods.
Standardization	Measure efficacy and ease of use across multiple users
Biocompatibility	Analysis of literature/standards

Societal expectations are primarily concerned with safety. The safety of the device can be ensured if the functions and requirements are appropriately fulfilled. The primary function that would address the issue of safety is efficacy. Here, efficacy ensures that the device will work and will not cause adverse health events (caused by infection or device failure) and will not cause further damage. In addition to safety, there has been a recently growing societal expectation of the biomedical industry improving quality and length of life. This expectation has been primarily driven by biomedical research and advancement. Consequently, this device is expected to contribute to this trend by having long-term efficacy and thereby improving overall health outcomes. Another societal concern is the cost burden. With the high cost and uncertainty associated with health insurance along with the continued globalization of the biomedical marketplace, the device is expected to be relatively cheap and accessible to all. The solution is therefore expected to have economic benefit over pre-existing methods and other competitors. Lastly, the device is expected to confer with legal and ethical standards that would allow its utilization without conflict. Ethically, the device should ensure sufficient safety and undergo appropriate clinical trials before implementation so as to abide by the Code of Ethics and FDA regulations. To coincide with safety and ethical regulations, the rights and respect of human and animal subjects must be maintained. Sufficient simulations should be performed where appropriate, so as to prevent unnecessary subject testing. Further, patient confidentiality must be maintained throughout the design and testing process.

The sources of project learning can be divided into two categories: research and action. The research component consisted of gathering knowledge from various sources including the stakeholder, professors, journal articles, and books. These sources helped lay the foundation for attaining all of the background information necessary for product success. This includes information about current anastomosis methods, biological information, novel products, and overall design recommendations. Following appropriate research, the team relied on experimentation for continued learning. This entailed experimenting with porcine intestine to learn about its size and mechanical properties. This allowed the team to produce rudimentary prototypes to analyze behavior and performance. With this information, the design could draw conclusions about the design, and the device could continue to be refined and optimized.

CONCEPT DEVELOPMENT

By analyzing the product landscape and comparing the successful and unsuccessful products, we decided on several different ways that we could approach the problem of performing anastomosis procedures. We explored each potential design solution to decide which design would create the best outcome while still remaining reliable and easy to use. We knew that we had a major time constraint to keep in mind, since we would only have one semester (roughly four months) to manufacture and test this product. We utilized the flowchart below (**Figure 1**) showing different approaches to the anastomosis problem to help us brainstorm different solutions that we could create for this unique design problem.

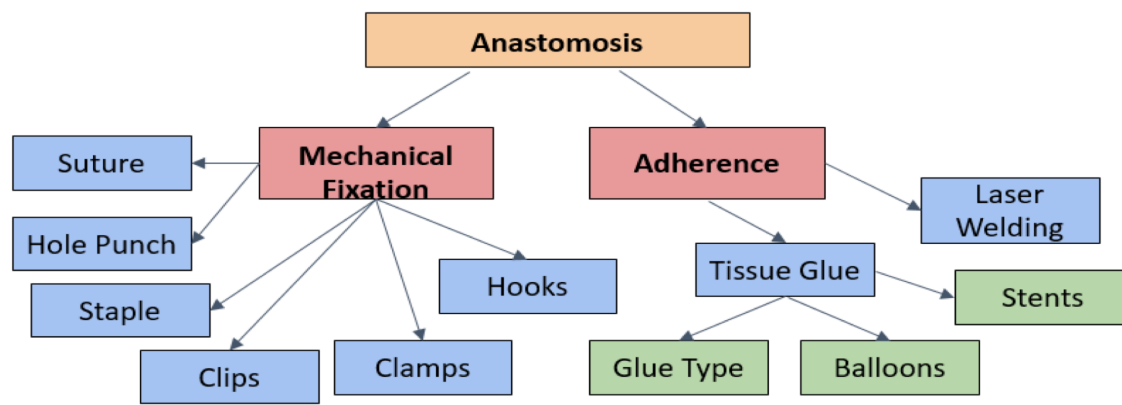


Figure 1. Flow Diagram of Design Concepts Considered. The design concepts could be divided into two broad mechanisms: mechanical fixation and adherence. Both of these attachment mechanisms could be further categorized as shown.

After extensive research, we devised two overall mechanisms for performing anastomosis procedures: mechanical fixation and adherence. The mechanical fixation method includes solutions such as sutures, staples, and hooks that would cinch or mechanically hold the ends of the intestines together. In cases that did not entail end-to-end anastomosis procedures, this mechanism would require a procedure to ensure appropriate hole and/or vessel size (such as a hole punch). In addition to mechanical fixation, the team also identified adherence as a potential mechanism for attachment. This could potentially entail gluing or welding the tissues together. With the adherence methods, however, a balloon or stent would likely be needed to provide stability to the underlying tissue. With this general outline, many solutions were considered within a complex construct; however, the best concepts either met a number of fundamental needs in a simple way or met all needs with a more complicated system. These two categories arose as front runners as a result of the simplistic ideology comprised of what will get the job done to an acceptable degree and above.

The first proposed concept was a T-shaped balloon that would be inserted through a hole in the vein graft and lowered down into an incision in the coronary artery for an end-to-side anastomosis. Once the balloon was inserted into the coronary artery, it would then be inflated and a BioGlue would be applied to the connecting point. However, for the device to be successful, it would need to be ensured that

the same length cut was made each time on the vessels. This led to a secondary potential design idea: inverse scissors. A pair of inverse scissors with blades on the outside and a locking mechanism that would allow for the blade to only open a certain length each time would allow for the same cut to be made each time.

With the goal of meeting the designated requirements, the concept of a “Reinforced Fixation Anastomotic Punch” was proposed for use in side-to-side anastomoses. This device would meet the requirements of ease of use, efficacy, biocompatibility and longevity through its multi-component approach. It would utilize a handheld device portion in conjunction with a surgeon placed anchor. The handheld portion would consist of a front graft vessel loading port, internal hole punch, topside bioactive adhesive canister dock, internal extrusion pathway, bottom face extrusion ports, and a button activated deployment system. The anchor would be inserted into the target vessel by the surgeon after an initial incision. It would then be grasped by prongs on the handheld device portion and thrust upward when the internal hole punch becomes activated. A mechanical fixation would be activated in coordination with the extrusion of the bioactive adhesive. The hole punch ensures that the holes created on the graft and target vessels are of the same proportions. The inserted anchor protects the opposite wall of the target vessel from puncture while also acting as the lower portion of the hole punch mechanism. The mechanical fixation ensures initial connection of the two vessels while the bioactive component reinforces the connection and ensures minimal leakage. The button activated approach ensures a simple and easy to understand process.

Another design concept considered was one that entails modifying the EEA stapler (**APPENDIX B**) to perform side-to-side anastomosis attachments. In doing so, the applicator end that attaches to the anvil would be moved to the side of the stem. The anvil would have nitinol arms that could extend and contract based on temperature. Thus, the anvil would be kept in a cold saline bath that would cause the nitinol arms to contract, making the anvil small enough to be placed in a slit in the target vessel. Once the anvil warms to body temperature, the nitinol arms would extend, allowing the component to be stabilized and anchored in the vessel. The applicator would be placed through the end of a grafted vein at which point it would attach to the anvil and fire. Firing of the device would entail hole punching and releasing staples. The anvil would prevent the staples from puncturing the back side of the target vessel, and would cause the staple arms to fold over. At this point, the anastomosis site would have to be flushed with cold saline to cause the anvil arms to contract. This would allow the device with attached anvil to be pulled out of the grafted vein. The grafted vein would then have to be ligated. This design would effectively hold together the two vessels and achieve the goal of standardization. Refer to **APPENDIX C.1** for a diagram of this solution.

A nitinol clamp similar to the Medtronic, Inc. U-Clip was also proposed for side-to-side anastomosis procedures. This would entail two rings that are connected by nitinol wire. At cooler temperatures (in a cold saline bath), the nitinol wire would be straightened and the rings would be separated. This would allow the device to be placed through a slit on the side of both target vessels. At body temperature, the nitinol wire would bend such that the rings are brought together, effectively holding the vessels together. Refer to **APPENDIX C.2** for appropriate drawings.

The final concept considered was a flared conduit, which was later refined to a lipped conduit, used in conjunction with mechanical and chemical fixations. Two tissue segments would be mounted in an end-to-end manner over the lipped ends onto the device stem until the segment ends contacted one another. Once the two ends of the intestines were touching, the BioGlue could be applied to the entire perimeter. The BioGlue would not only work to prevent leakage, but it will also promote the healing of the anastomosis site. A clamp would then be used to mechanically fix the conduit in place, and support the union of the two sides of the intestines. This simple approach achieves the desired ease of use stipulation. The double fixation method should ensure the efficacy of the connection. The conduit and clamp would be composed of 85:15 PLGA, a biodegradable material which would be excreted from the body after tissue union is achieved. The BioGlue will stimulate tissue union and be used by the surrounding tissues in that effort. The degradability and resorption of the materials will achieve the necessary longevity of the connection as they will allow for a newly formed tissue connection while leaving no foreign material within the body. PLGA is a co-polymer that is commonly used in the body as absorbable sutures, so this will ensure that there will be a minimal reaction to the foreign body. This method achieves the main goals necessitated by the stakeholder while maintaining an overall simplicity of design.

The process for choosing the best product was grounded in the stakeholder needs and project constraints. When mechanical fixations are used that puncture the vessel and glue is applied, the glue will seep through the puncture. For this reason, devices combining glue and tissue punctures were eliminated (“Reinforced Fixation Anastomotic Punch”). On the other hand, the efficacy of glue alone to hold together two vessels alone could not be determined, so relying on a mechanical and adhesive connection seemed optimal. In addition, simplicity was stressed during the design selection process. To make a successful design, given the limiting constraint of time, the chosen device needed to be simple for ease of production, manufacturing, and testing. For a more comprehensive breakdown and screening matrix, see **APPENDIX D**. The screening procedure indicated that the conduit design with adhesive would most adequately address the stakeholder needs. However, certain modifications needed to be made to improve the efficacy and simplicity of the overall procedure. In an effort to eliminate the need to account for blood-contacting surfaces, the overall project was refined to apply to intestinal anastomosis. The full design description is described in the following section.

PRODUCT DESCRIPTION

Product General Description

Once the decision was made to use the conduit design rather than the other methods described in the previous section, there were several factors we needed to examine in terms of the overall design. The first thing we had to decide was the length of the conduit. We wanted it to be large enough to allow passage for the necessary materials to pass through the bowel, while small enough to not stretch and damage the tissue. Along with the length and internal diameter of the conduit, we also had to decide on the diameter of the conduit lip. With this decision, we had to consider the fact that the lip needs to prevent leakage from the intestine by physically blocking the fluid and material from seeping into the area between the lips. We also, once again, did not want the pressure from the conduit to damage the tissue which could lead to future issues that will probably require surgery.

There are several key components that are incorporated into the conduit that are essential for its proper function. The first feature for the conduit is the lip design. The lip is essential for helping reduce the amount of movement of the conduit while implanted in the intestines. Though we are testing this device on the large bowel, it has potential to be incorporated into the small intestines, esophagus, and even vascular. With all of these locations, it is essential that the conduit stays in place and is not allowed to move. With that in mind, a larger diameter lip was incorporated into both ends of the conduit. This would work in cooperation with a clamp device that is applied around the intestines after the conduit is implanted and the glue is applied. Thus, the force from the intestines keeps the conduit in place, and the external clamp (with a diameter slightly less than that of the lips) makes it impossible for the conduit to move while the clamp is secure. Another essential function of the conduit lip is the reduction of contents from the intestine being able to interfere with the anastomosis site due to the tight space between the lips and the intestine, blocking matter from passage. With the internal components of the intestines being acidic or basic depending on the section, it is important for those materials not leak out. With that in mind, the conduit outer rims are designed to be slightly larger in diameter than the intestines (which works due to the elasticity of the intestines) so that the intestines can stretch over the conduit and be secure and tight at the site of the lips. This feature allows for minimal passage of contents into the space between the outer rims of the conduit, thus less interference at the site of anastomosis.

Product Dimensions

After doing research, we initially decided that the conduit lip needed to have a diameter of 3.5 inches and the internal section needed a diameter of 3 inches. This was decided based on the average human intestine diameter of 3 inches. Upon receiving the prototype, we quickly determined this measurement was far too large. We reduced the diameter of the lips from 3.5 to 2.5 inches and the internal diameter from 3 to 2 inches. After doing a quick print using a basic desktop printer, we decided to reduce this even further to around 2.2 inches for the outer lip and 1.6 inches for the inner diameter. The appropriate device measurements were determined by using a pair of calipers to determine the diameter of porcine large intestines. Once the first round of testing was completed, we decided to keep the internal diameter the same while reducing the outer diameter to 1.95 inches. These were the dimensions used in the final round of testing for our prototype device and the final conduit can be seen in **Figure 2**.

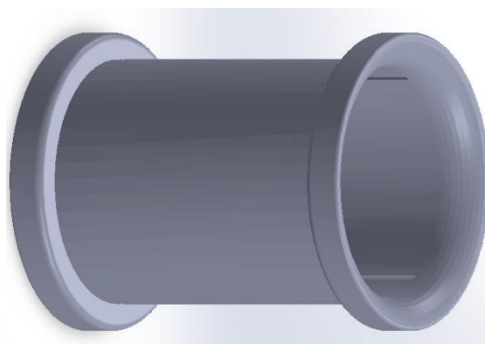


Figure 2. Final Conduit Design. Final design of the conduit, to be placed inside the intestines. This component has an internal facing lumen and an external facing intestinal wall.

Product Material and Degradation Properties

Another key concept for the device is the material that is used for the conduit and clamp assembly (**Figure 3**). The first decision that had to be made was whether or not we wanted the assembly to be permanent or not. If permanent, the device would have to be sufficiently biocompatible to maintain viability in the body long-term, and the foreign body response would need to be minimal. If not permanent, it must be degradable so that only one surgery is needed, and it must degrade within a time frame that allows enough time for the anastomosis to be complete. The initial decision was to make the device permanent and use Polytetrafluoroethylene (PTFE) due to its superior biocompatibility, low coefficient of friction (allowing material in the lumen of the intestines to adequately pass through), and lack of reaction with tissue. Upon discussion with Dr. Lee, however, it was decided to make the device biodegradable. After careful research, it was decided to use Poly Lactic-co-Glycolic Acid (PLGA) copolymer. The advantage of using PLGA is the ability to tailor device properties by altering polymer composition (PGA is more amorphous and degrades quickly in the body while PLA is more crystalline and has a lower degradation rate). Thus, when combined into a copolymer, the degradation rate can be manipulated based on the composition. Upon research, it was decided that PLGA 85:15 would be used. With PLGA 85:15, the degradation rate is around 6-8 months²², which gives plenty of time for the anastomosis to be complete. The final device will be mass-produced using injection molding, which allows for relatively cheap production in a time efficient manner after the initial investment of the molds.

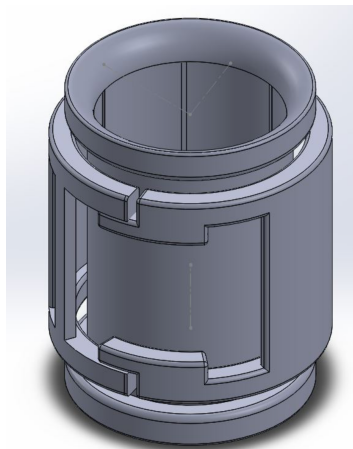


Figure 3. Final Design of the Conduit-Clamp Assembly. Once in place, the intestines would wrap around the conduit and BioGlue® would be applied. After the BioGlue® sets, the clamp assembly would be administered.

Another key component to the device in terms of degradation are the channels implemented into the conduit. Since the conduit is designed to degrade in the intestines, the degradation must be controlled so that large chunks don't degrade off that could be sharp and cause damage or even blockage further downstream. With that in mind, it is very important that we manipulate the design of the conduit so that the chunks from degradation are not too large inside of the intestines. Channels were incorporated on the internal surface of the conduit so that certain portions of the conduit were thinner and would thus degrade faster. These channels were designed so that the conduit would degrade into small square pieces rather than large chunks. These small square pieces would have no trouble being passed through as opposed to the large chunks, thus reducing further possible damage.

As discussed earlier, one of the main features of this device is the two-part system of a clamp and conduit. The clamp is composed of the same 85:15 PLGA copolymer and is placed on the outside of the intestines in order to secure the conduit in place. When designing the clamps, the initial design was a single piece clamp that relied on a small amount of force from the surgeon by pressing the opening to the section of the intestines (with the conduit inside) so that the clamp would deform and slide over the conduit and then spring back into place once the opening reached the other side of the conduit. An illustration of this initial clamp is shown in **APPENDIX E**. After discussion with Dr. Lee, we were unsure if this design would lead to tissue damage due to the force placed on the intestines against the conduit and it was decided to explore other options for the application of the conduit. That led to the development of the two-part hinged clamp which allows for minimal force to be placed on the intestines during application while also maintaining a secure fit with minimal possibility of displacement.

The hinged clamp is composed of two parts, each with male and female pieces that when attached at one end, create the hinge. Once the hinged clamp is attached at the other end, it allows for minimal movement, thus, providing a secure clamp when placed on the outside of the conduit. The design of the clamps male parts include a fillet at the base in order to provide high strength and prevent them from breaking off and the same fillet was then added to the female part in order to allow for the male part to fit. The hinged clamp design gives the surgeon great ease of use when applying the device and only a minimal amount of force by the surgeon is needed for application. The clamp fits around the central portion of the conduit and the diameter of the clamp (when in place) is less than the diameter of the conduit lip, making it impossible for the conduit to pass through the clamp. Supports are added to the outer clamp component (**Figure 4A**) that are on the outside of the fixture so that only the inner clamp component (**Figure 4B**) must be deformed when applying to reduce possibility of them coming apart.

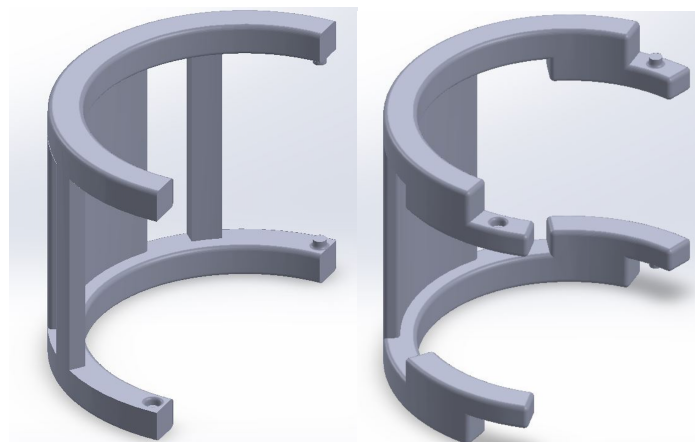


Figure 4A and 4B. Final Design of the two-part clamp system. The final clamp has two components that are both applied to the outside of the intestines and hold the conduit in place. A. The component on the left is the outer clamp component. B The figure on the right is the inner clamp component.

The final key component of the design is the application of the tissue adhesive on the outside of the anastomosis site which allows for the ends of the intestines to be held in place and touching one another in order to promote closure. This also provides an additional protection from leakage of the intestinal contents which further reduces the chance of an additional surgery being needed and infection. The first

adhesive looked into was TissueGlue, but with little testing being done on the intestinal area and high cost, we decided on CryoLife BioGlue® (**Figure 5**) instead. CryoLife BioGlue® has been used on soft tissue and intestines in Europe and would provide a way to prevent leakage for our device as well as make sure the ends are held tightly together to promote growth. Testing was done on the intestines with and without the conduit and it was determined that the BioGlue was capable of withstanding over 15 Newtons of force for both tests and prevented any leakage from occurring. As a result, BioGlue was determined to be a suitable adhesive for our device.



Figure 5. CryoLife BioGlue® and Applicator. This tissue adhesive would be applied to the intestines once they have been wrapped over the conduit. This provides an extra layer of protection against leakage.

DESIGN EVALUATION

The various requirements the device was to meet required a range of verification methods. These verification methods included materials research, device assembly practice, and basic testing. The materials research was performed to gather information on our intended final design material (PLGA 85:15) and to find a comparable prototype material for testing. Eventually it was determined from available literature that PLGA 85:15 is an FDA approved material with a degradation time of 6-8 months. This met our requirement of biocompatibility as the material has previously been proven to result in no significant detrimental host response. The material also meets the requirements of degradability as well as durability as it degrades in 6-8 months which is well outside the necessary window for anastomotic healing. As the anastomosis connection will have unionized prior to the theoretical degradation of the conduit, the durability is ensured throughout the healing process. Additionally, PLGA 85:15 can be injection molded, providing an easily translatable mass production method for a final product at costs as low as approximately \$367 per device. Initial production costs would be around \$2,100 per device, but this is predicted to drop steeply to the mass production estimate. While the basic research is sufficient for initial prototype direction, actual degradation studies would need to be performed to ascertain the true degradation rate of our device given its unique architecture.

It was also determined that an ABS/polypropylene blend available from Protolabs® by the name of Accura® Xtreme™ White 200 possessed mechanical properties comparable to PLGA 85:15. This led to its use as the material from which the final prototype was produced, illustrated in **Table 2**. This final prototype was the device used for testing the remaining needs including ease of use, comparable application time, efficacy, and leakage reduction. Prototype costs are consistent and remain around \$500 per entire device assembly.

Table 2. Material Property Comparison Chart. Comparison of the material properties and elasticity of the human intestines and device materials. 85:15 PLGA corresponds to the theoretical, final design material and Accura® Xtreme™ White 200 corresponds to the prototype material.

	Human Large Intestines ^{23, 24}	85:15 PLGA ²⁵	Accura® Xtreme™ White 200 ²⁶
Young's Modulus (MPa)	0.9 - 5.18	2.0×10^3	2.4×10^3
Elongation (%)	80 - 180	3 - 5	7 - 20

Concerning the standardization, ease of use, and time of application, the Team Connect members each performed an anastomotic simulation, with another team member's assistance, with our device procedure and assembly using porcine intestines. The time from simulation initiation to complete device application for each team member stayed at approximately 3 minutes. Despite the limited sample pool, simulation completion times averaging 3 minutes using unskilled workers lends to the belief that surgeons in the operating room could improve on, or at the very least match, this application time. As the applications times were similarly short across all members, the device and application process were demonstrated to be simple, easy to implement, comparable to duration of current methods, and capable of standardization.

Additionally, the efficacy of the device had to be tested concerning its durability against internal forces and its resistance to leakage. In order to test the assembly's ability to withstand forces and resist rupture at the site of intestinal union, the full assembly, with mounted intestines, was subjected to tensile forces. The test was administered by attaching a luggage scale to the far end of one of the attached intestinal segments. The scale was attached to the segment by using the scale's prongs to pierce the intestinal wall and then wrapping the far end of the segment around the prongs of the scale to further secure the connection. The scale was mounted onto a secure lab station, and the intestinal segment mounted to the other side of the conduit was slowly pulled by hand until the intestinal connection ruptured. Six tensile tests were performed with comparable results. In each case, the intestines began tearing at the luggage scale prior to rupture of the intestinal connection. The final force required to rupture the bond at the connection site was approximately 25 N across all tests. As the intestines themselves began to tear prior to bond rupture, it is safe to assume that the bond will hold strong, at least in the face of mechanical forces, within the intestinal environment.

As a bioadhesive was used to secure the intestinal connection at the center point, additional tensile testing was required to determine the device's contribution. The tensile testing was performed without the device assembly, and the only factor securing the connection was the adhesive. The tests were performed in the same manner mentioned above, and the force required to rupture the connection was approximately 17.5 N. As this rupture force is smaller than the one found when the full device assembly has been implemented within the anastomosis, it can be assumed that the conduit and clamp of the assembly further secure and reinforce the connection.

Also, as the device will be used to attach intestinal segments, it must provide a sound and secure connection to prevent leakage of any intestinal fluids. To determine the device's ability to prevent leakage

of any fluid, the simulated anastomosis was performed with the intestinal segments, and then fluids were sent through the length of the mounted intestines by manual pouring into an elevated intestine position. Leaked fluids were to be collected within a graduated beaker positioned directly below the connection; however, upon testing with proper application, no fluids were leaked. The two fluids tested were water and a chocolate cookie milkshake to provide varied possible viscosities. Some leakage was witnessed on one run where the adhesive had not been applied entirely around the connection. This suggests that the lips of the conduit should be expanded to provide a tighter seal at the ends of the mounted intestinal portions to reduce reliance on the bioadhesive used.

Finally, as all patients will not conform to a single intestinal diameter, it is imperative to provide a sizing solution. Due to the nature of the production methods to be implemented, several sizes and iterations can easily be produced and kept in stock in large quantities. An inventory should be kept of available sizes, and the appropriate size-match should be used once the patient's intestinal dimensions are determined by either imaging prior to surgery or an additional sizer device used during surgery. The sizer device would be a conical shape with a stepwise increase in diameters which could be inserted into the resectioned intestines to determine the required corresponding conduit assembly. Simple calipers should be used to determine intestinal wall thickness. The conical sizer device will allow for patient specific conduit assembly sizing and will allow for an appropriate fit to meet our previously mentioned requirements.

RECOMMENDATIONS & FUTURE WORK

This product has been able to circumvent all of the pitfalls associated with the products and procedures that are in use today. Not only is this device extremely easy to use, it is effective. The issue of stricture is mitigated by the internal conduit that will hold the anastomosis site open while the healing occurs. This product will also reduce leakage. There was no leakage observed with our device when water and a thicker medium (a milkshake) was used. This assures us that viscous or more watery sections of waste will not be able to leak out of the site while it heals. Our tensile tests have also assured us that there will be no failure of the BioGlue/conduit combination due to any stresses that the body will be able to put on the assembly. This is because the BioGlue alone failed at 17.5N, and when the assembly was tried, the integrity of the intestines failed first.

Additionally, this method is also time effective. Each assembly time took roughly 3 minutes to complete, which is similar to the amount of time it takes to deploy staplers and it is faster than the hand suturing method. This provided support that the design can standardize the anastomosis process. Finally, this device is cost effective. Once the molds are created, the cost for the raw materials to create the product will cost about \$2,100 when the material is not purchased at bulk price. When the device is mass produced, the cost for the raw material will be greatly decreased, decreasing the price of each assembly.

The future of this product will involve improving the ergonomics of the device and overall refinement of the design. The initial refinement would be to find the perfect balance of how tall the lips of the conduit should be to create an adequate seal around the intestines, but to not stretch them too far and cause necrosis. This would involve getting a better estimate of the diameter of the intestines with and without waste in them, to observe the state that the surgeon would be administering the device in and to

also see how our device would work when the intestines are in their natural state. Further, this would involve creating various sizes for the different sizes of intestines encountered, and eventually for different surgeries (esophageal, gastric bypass, small bowel, etc.) Additionally, we would need to find a way to effectively characterize the different sizes and which assembly would be needed for each size. This could either be achieved through imaging or with a completely separate device that would be used in the operating room.

There is still further testing that needs to be performed to ensure the success of this device. Degradation tests need to be performed to observe how the conduit and the clamp will degrade since one will be inside the intestine and one will be outside of the intestine. The inflammatory response to this material will also need to be measured. Another important test would be to find the most effective sterilization method for our device. Ethylene oxide and irradiation methods are both used on this material to sterilize it, but tests on the most efficient method that can be used without harming the integrity of the product would be needed in the future.

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APPENDIX A

While doing research for this project, we knew that there were many existing products on the market already. We decided that the best way for us to tackle this problem would be for us to see what has already been done and analyze the strengths and weaknesses of all of the other products. After analyzing these products, we would attempt to combine all of them in a way to eliminate most of the weaknesses. This gives us a better understanding of what works and what will not work, as well. A few of the various products that we researched include: Periclose, Inc. Heartflo device, Medtronic, Inc. U-Clip, United States Surgical Corporation One-Shot system, St. Jude Medical ATG Distal Coronary Connector, and St. Jude Medical Symmetry Bypass System Aortic Connector.

Periclose, Inc. Heartflo device: While using this device, the sutures still have to be tied after the device is used, which only eliminates a couple of steps that the surgeon has to perform. This also means that this device is not completely automated. Arteries smaller than 1.8mm cannot be used, which is a major limitation of this device. The “square-shaped foot” of the device is cumbersome to use with small vessels. Supplementary stitches are needed to achieve complete hemostasis, which, again, means that the device is not fully automated. One strength of this device is that it does leave less endovascular material behind than other devices do. Some of the weaknesses of this device include: no procedure time difference compared to hand-suturing (15-22 min.), extensive handling, size limitation, shape, additional suturing required.

Medtronic, Inc. U-Clip: The U-Clip is a device manufactured by Medtronic. The mean usage time was about 8.6 minutes, which is comparable to the time it takes to hand suture. The device is relatively easy to use, as reported by studies of surgeons that have used this device. This device requires no additional knot tying. There is a concern about this device due to nitinol allergies of some patients, which may be unknown until the device is implanted. This device also comes with a higher cost. Some of the major strengths of this device are that it is useful for distal and proximal anastomosis procedures, it has excellent clinical patency, and interrupted anastomosis causes less deformation. Nitinol is a superelastic, shape memory alloy that allows a device to be deformed, but return to its original shape after warming to body temperature. However, the weaknesses of this device include the nitinol allergies and the higher cost associated with the device. The design team considered a nitinol clamp that would hold the two vessels together.

United States Surgical Corporation One-Shot system: The One-Shot Device creates rapid and reproducible constructs. This device can be used in vessels as small as 1.8mm, which is a limitation since these vessels may be much smaller. The device has reported that diseased artery would be prone to dissection, which is a major problem because most of the patients that would require this device would have diseased arteries. Due to this, the device requires a flexible arterial wall. There is also a learning curve associated with this device, which many doctors would be hesitant in committing time to. The proximal side has to be done first and it leaves the distal end free.

St. Jude Medical ATG Distal Coronary Connector: This device consists of a stainless steel clip that is attached to a balloon delivery catheter. The balloon design provides expansion/contraction capabilities of the device and provides the device's deployment mechanism. The catheter is inserted through the distal end of the conduit and advanced to the anastomosis site on the vein. A small incision should be made at this site, and the catheter is slid through the hole. The balloon is subsequently inflated and the stainless steel connectors are deployed, thus attaching to the conduit. A small incision is then made in the coronary artery and the nosecone of the device is advanced, exposing the other end of the of the connectors. Expanding the balloon causes the hooks to attach to the artery and join the vessels together, at which point that catheter system can be removed and the end of the conduit is ligated. The

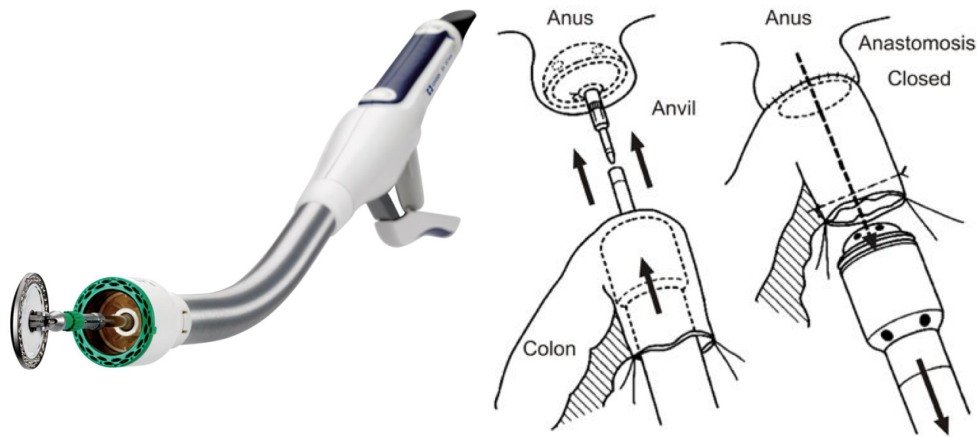
strengths of this device are the short loading/preparation time (~2 min.), the short deployment/procedure time (~2 min.), there is instantaneous hemostasis, and maintained appropriate fluid flow. The weakness of this device include the minimum diameter of 2.0 mm, stainless steel connectors require careful handling to prevent distortion, 1 in 5 had to be removed due to leakage, there is a potential foreign body response due to introduction of foreign material into intima of vessels, endothelial damage.

St. Jude Medical Symmetry Bypass System Aortic Connector is a device that can connect grafts with diameters from 4.5mm to 6mm. There is no clamping of the aorta necessary to use this device. The time to complete the mechanical anastomosis was 10 seconds; loading time takes up to 16 minutes, which is comparable to the amount of time that it takes to hand suture. This device is reliable and easy to handle. The aortic puncher used creates round holes. The graft must be administered at a 90 degree angle from the aorta, limiting the number of grafts that can be performed and can possibly lead to kinking of the graft.

Almost all intestinal anastomoses are currently performed using staplers. These devices provide a quick and easy way to create an anastomosis, especially when used laparoscopically. Some issues associated with these devices are that there is a great amount of shear stress that is put on the tissues when staples are used. They are generally made out of a material that is not biodegradable, so they will stay in the body and have the potential to create a foreign body response at the anastomosis site. There is also the possibility of the staples misfiring or missing the target tissue, making them ineffective. If this happens, or the stress put on these staples is too great, there is a chance that the anastomosis site could open up and there could be leakage from the intestines to the area outside, which could create many problems. This increases the chances that the patient will have to have another surgery, and it opens them up to an added risk of infection. For these anastomoses, there is not so much a risk that they will occlude, but there is a potential that they will shrink in diameter at the site of the anastomosis, which makes the chance of a blockage occurring greater. There needs to be a better, more efficient way to create these anastomoses.

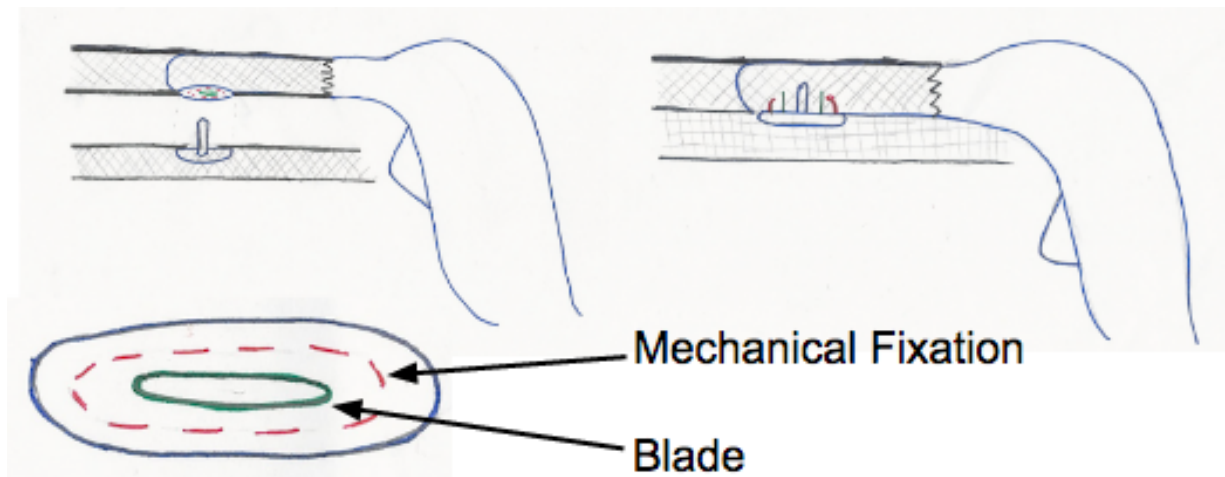
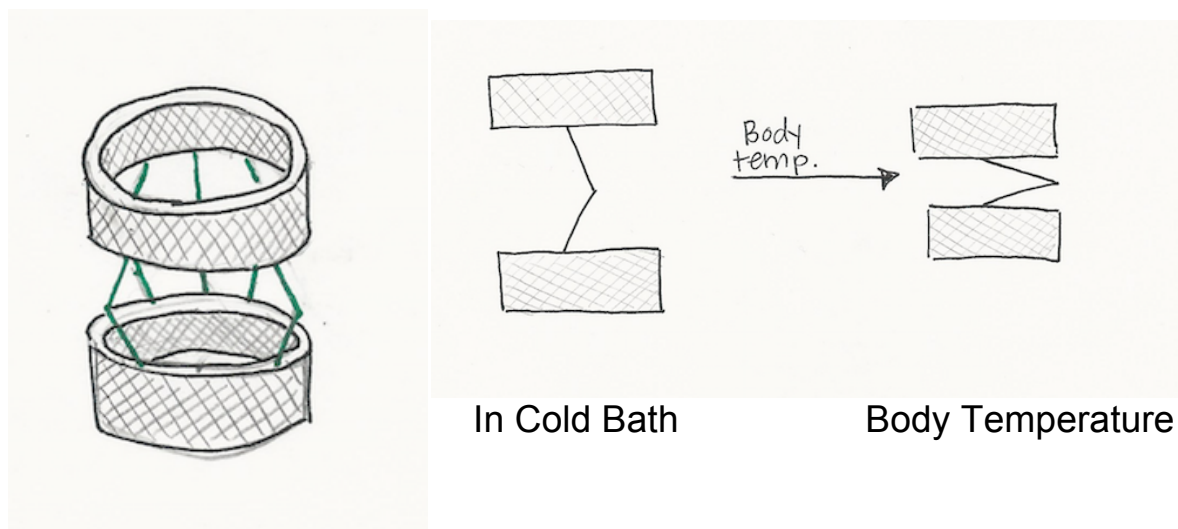
Medtronic, Inc. EEA Stapler is a stapler that is used for end-to-end anastomosis for colorectal procedures. This device is a two component system, consisting of the staple applicator and an anvil. The anvil is placed in the end of the target vessel, such that the tip is pointed towards the other vessel being attached. The applicator is a device with a long stem and attachment mechanism at the end.

OptiFlow® Vascular Anastomotic System has received CE approval and is intended to be used for hemodialysis.¹⁸⁻²¹ The conduit design is made of a non-thrombogenic siliconized polyurethane that has ridges allowing it to be placed inside the vein and a flanged end that is placed inside the artery. Users of this device have reported standardized, shortened procedure times without thrombosis or leakage.¹⁸⁻²⁰ However, there is still concern regarding dislodging and long-term efficacy.²¹

APPENDIX B

[1] DST Series™ EEA™ Staplers (<http://www.medtronic.com/covidien/products/surgical-stapling/circular-staplers>)

[2] DST Series™ EEA™ Stapler in use for Colorectal Surgery
(<http://www.coloproctol.org/search.php?where=aview&id=10.3393/jksc.2008.24.1.62&code=0009JKSC&vmode=PUBREADER>)

APPENDIX C.1**APPENDIX C.2**

APPENDIX D

Biocompatibility, suture/staple-less, ease of use, efficacy, and simplicity were chosen as primary categories by which to “grade” the designs. Each of these categories appropriately reflects stakeholder needs and constraints of the project. Devices that entailed leaving nitinol in the body were graded moderately for biocompatibility due to the potential of nickel allergies. Ease of use was determined by estimating the number of components that the surgeon would have to interact with to perform the anastomosis procedure. Simplicity was graded by analyzing the number of components and materials comprising the system and estimating the level of difficulty in manufacturing and refining the design. For efficacy, devices that solely relied on staples for the attachment were graded poorly. Devices that only relied on glue or entailed combining glue with puncture mechanisms were graded moderately due to question about the efficacy of adhesives. The inverse scissors were graded “n/a” for biocompatibility and suture/staple-less because they are not intended to be left in the body. In addition, they were graded “No” for efficacy because they are not involved in actually holding vessels together. Thus, it can be seen that the conduit design best addresses each of the needs and constraints.

	Biocompatible	Suture/ Staple-less	Ease of Use	Predicted Attachment Efficacy	Simplicity
Inverse Scissors	n/a	n/a	Yes	No	Moderately
Nitinol Clamps	Moderately	Yes	Yes	Moderately	Moderately
Modified EEA	Yes	No	Moderately	No	No
Balloon with Bioglue	Yes	Yes	Moderately	Moderately	Moderately
Conduit	Yes	Yes	Yes	Yes	Yes
Reinforced Stent	Yes	Yes	Yes	Moderately	Moderately
Reinforced Anastomotic Punch	Yes	Moderately	Yes	Moderately	No

APPENDIX E

Initial Clamp and Assembly

