

Pilot Study of Robotic-Assisted Harvest of the Latissimus Dorsi Muscles

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A Single-Center, Non-Randomized, Prospective Study of the da Vinci® surgical system in Latissimus Dorsi Muscle Harvest Procedures

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1 PROTOCOL SUMMARY

- Title:** Pilot Study of Robotic-Assisted Harvest of the Latissimus Dorsi Muscles.
- Design:** Single-Center, Non-Randomized, Prospective Study of the *da Vinci® surgical system* in Latissimus Dorsi Muscle Flap Harvest Procedures.
- Purpose:** To evaluate the safety and feasibility of the *da Vinci® surgical system* in minimally invasive muscle flap harvest procedures.
- Enrollment and Sites:** A maximum of 15 subjects requiring a muscle flap harvest for subsequent breast, scalp, upper extremity, or lower extremity reconstructive surgery will be enrolled at The University of Texas MD Anderson Cancer Center (MD Anderson) in Houston, Texas.
- Study Duration:** Initial Enrollment: Q1'15
Last Enrollment: Q2'17
Last Follow up: Q4'17
- Subject Follow up:** 0-2 weeks, 2-4 weeks, 1-3 months, and 3-6 months post-procedure.
- Study Endpoints:** Primary Safety Endpoint:
The primary safety endpoint is muscle flap failure.
- Secondary Endpoints:
1. Evaluation of donor site complications through 6 months post-procedure.
 2. If the flap is for external use, interval viability with a Doppler proximally and distally will be checked at 3 months post-procedure.
 3. If the flap is for pedicled, internal use over an implant, no additional evaluation will be possible unless planned or unplanned reoperation exposes the muscle, at which

time a Doppler evaluation would be undertaken.

4. Conversion rate (i.e., completion of the latissimus dorsi harvest procedure with the *da Vinci® Robotic Surgical system* without converting to an open procedure).
5. The validated QuickDASH questionnaire to evaluate postoperative shoulder function as compared to preoperative QuickDASH shoulder function.
6. Postoperative pain assessed by validated visual analog scale (VAS).
7. Physical therapy assessment of range of motion and strength of the affected shoulder using the validated American Shoulder and Elbow Surgeons (ASES) assessment tool.
8. Length of stay and analgesic use to be compared to historical controls of the open procedure.

**Study Inclusion
Criteria:**

1. The subject must be equal to or greater than 18 years of age.
2. The subject must be willing and able to provide informed consent.
3. The subject is willing and able to comply with the study protocol.
4. The subject is undergoing one of the following reconstructive procedures that requires latissimus dorsi muscle harvest:
 - a. Post-mastectomy breast reconstruction procedure (either nipple or skin sparing) in which a female subject needs additional muscle coverage over an implant, but does not need additional skin (i.e., patient is a candidate for a pedicled latissimus dorsi muscle flap procedure); OR,
 - b. Scalp reconstruction procedure in which the subject needs a free latissimus dorsi muscle flap for wound coverage; OR,
 - c. Upper extremity reconstruction procedure in which the subject needs a free latissimus dorsi muscle flap for wound coverage; OR,
 - d. Lower extremity reconstruction procedure in which the subject needs a free latissimus dorsi

muscle flap for wound coverage.

5. The subject agrees to follow up examinations out to 6 months post-procedure.

Study Exclusion Criteria:

1. The subject has a BMI > 35.
2. The subject has a history of significant bleeding disorders.
3. The subject is diabetic.
4. The subject is known or suspected to be pregnant or lactating.
5. The subject has a history of peripheral vascular disease.
6. The subject is a current smoker (has smoked within 4 weeks prior to surgery).
7. The subject has had prior back or axillary surgeries which could compromise the blood supply of the flap.

Study Monitor:

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2 INTRODUCTION

The purpose of this clinical study is to evaluate the safety and feasibility of the *da Vinci*® surgical system used in minimally invasive muscle harvest of either a free or pedicled

latissimus dorsi muscle. In this study, the harvested muscle will be used in breast, scalp, upper extremity or lower extremity reconstruction procedures as these are anticipated to be the highest volume use for these muscle flaps. However, the procedure under study is for robotic-assisted muscle harvest only, not the subsequent manually performed surgical reconstruction. Any type of reconstruction for which a free or pedicled latissimus dorsi flap is deemed to be medically necessary would benefit from this potentially less invasive harvest. As such, the endpoints of the study are aimed at evaluating safety, donor site morbidity, and the integrity and viability of the harvested muscle prior to the reconstruction procedure. The *da Vinci*® robotic surgical system is intended to assist in the accurate control of surgical endoscopic instruments. The system is currently FDA cleared for a variety of urologic, gynecologic, cardiothoracic and transoral otolaryngologic procedures. However, the device has not been specifically evaluated for latissimus dorsi muscle flap harvest. As such, the purpose of this study is to evaluate the safety and feasibility of the *da Vinci*® robotic surgical system for use in this specific procedure.

This is a prospective, non-randomized, single-arm study that will be conducted at The University of Texas MD Anderson Cancer Center (MD Anderson) in Houston, Texas. Up to 15 subjects requiring latissimus dorsi muscle harvest in conjunction with breast, scalp, upper extremity or lower extremity reconstructive procedures will be enrolled. The primary safety objective of this study is to evaluate the muscle flap failure. The efficacy endpoint is to assess flap viability at harvest via doppler and clinical examination. Secondary efficacy endpoints include postoperative assessment through quantitative (QuickDASH questionnaire), pain assessment (VAS), and a Physical Therapy assessment of the patient's range of motion and strength of the shoulder from which the latissimus dorsi muscle was harvested. All enrolled subjects will have four follow up visits (at 0-2 weeks, 2-4 weeks, between 1-3 months, and between 3-6 months post-procedure). The following section provides background information regarding current surgical methods for muscle flap harvest procedures.

3 BACKGROUND

3.1 Worldwide Clinical Usage of the *da Vinci*® Robotic Surgical system

The *da Vinci*® surgical system (s) is a robotic platform for minimally invasive surgery initially cleared by the U.S. Food and Drug Administration (FDA) for use in general laparoscopic surgery in 2000. Since then, it has received numerous clearances for a variety of indications for use, including general surgery, urologic, gynaecologic, thoracic, cardiac, and pediatric surgery. The *da Vinci*® robotic surgical system(s) has provided surgeons with the clinical and technical capabilities of traditional open surgery while enabling them to operate through small incisions. Each tiny incision (approximately 1cm), or port, involves insertion of an instrument which may be independently controlled by a

robotic arm on the *da Vinci*® robotic surgical system's patient-side cart. Robotic-assisted surgery may provide benefits to the patient including, but not limited to, shorter hospital stays, reduced rates of complications and a quicker return to normal activities as compared to open surgery.

From 2000 to present, over 800,000 robotic procedures facilitated by *da Vinci*® surgical system have been performed across a broad spectrum of surgical specialties around the world. Over 40 510(k) s have been FDA cleared for various device modifications and new indications for use. This commercial experience demonstrates the wide applicability of the system for use in common surgical tasks such as grasping, cutting, dissection, coagulation, etc. No new types of surgical tasks, or new instrument types will be required for use of the system in latissimus dorsi flap harvest procedures.

3.2 Literature Review - Latissimus Dorsi Muscle Harvest Procedures

Plastic surgeons frequently transport vascularized muscle from one part of the body to another, either as a free flap, in the case of lower extremity or scalp coverage, or as a pedicled flap, in the case of breast reconstruction and chest wall reconstruction. One of the most common muscle flaps employed to this end is the latissimus dorsi muscle flap. One problem with the harvest of this large muscle during an open surgical procedure is that the donor incision required to remove it from the orthotopic position is generally around 25 cm – 30 cm. For reconstructing, when overlying skin is a necessary part of the intended reconstruction, the harvest incision doubles as the skin harvest site. However, where only the muscle is required, the large skin incision is only for access and affords no benefit to the patient. Such procedures leave an unnecessary, long, conspicuous scar on the patient's back or flank.

In an effort to reduce unnecessary donor site incisions and related morbidity, endoscopic techniques for latissimus dorsi muscle harvest have been developed to reduce the amount of scarring associated with open procedures. Several authors have reported on these endoscopic techniques for free and pedicled flap harvesting^{1,5}. The endoscopic approach has been abandoned in many centers as a result of technical challenges posed by cumbersome instrumentation, and more sophisticated instrumentation has been deemed necessary to facilitate the endoscopic approach in the subcutaneous space⁷.

The following two sections discuss the current literature on endoscopic harvest of latissimus dorsi flaps and the utility of pedicled and free latissimus dorsi (muscle only) flaps, respectively.

Endoscopic Pedicled Latissimus Dorsi Flap for Breast Reconstruction

In 2007, Missana, et al reported on the results from a study of 52 patients who underwent latissimus dorsi endoscopic harvest for immediate breast reconstruction after a skin-sparing mastectomy¹. The authors developed this technique to decrease the morbidity of the donor site. The technique involves preparation of the site with lighted forceps, followed by endoscopic dissection after a neocavity is formed by insufflating CO₂. The mean surgical endoscopic time was 64 minutes and there was one procedure that converted to an open procedure. Complications included: 2 hematomas, 6 inflammatory syndromes and 1 pulmonary embolism. While 4 patients had skin flap necrosis during the reconstruction portion of the case, none of the patients had donor site necrosis complications during the latissimus dorsi flap harvest. The average length of hospital stay was 5.6 days. The dorsal drain was removed 15 days post-procedure. The authors concluded that endoscopic harvesting of the latissimus dorsi flap performed using the prescribed technique is feasible, reproducible and permits a significant reduction of incision size (2 cm as compared 20 cm with open surgery) and postoperative pain with good aesthetic results. The authors noted that this procedure was not recommended for patients who are overweight or in patients who smoke because of the significant rate of necrosis in the anterior thoracic cutaneous flaps.

In 2000, Ramakrishnan et al reported on 12 patients requesting breast reconstruction of a “high-risk” chest wall⁴. Endoscopic latissimus dorsi muscle harvest was conducted to cover an expander placed within an endoscopically created chest wall pocket. Of the 11 patients who underwent an oncological procedure, 8 of these patients received radiation therapy and 5 received chemotherapy. Additionally, 5 of these patients were smokers who smoked more than 10 cigarettes per day. Five of the 12 operations were performed through single-port access and the remaining 7 were performed with the addition of a bra strap port. Based on this case series, the authors advocated the use of two ports for operational ease and efficiency. The best muscle harvest time achieved was 60 minutes. Five of the 12 patients received blood transfusions; in all of these patients, the procedure had been initially attempted through a single port. While the authors noted acceptable results with their endoscopic technique, they concluded that improved instrumentation concerning the creation and maintenance of optical space would need to be developed before this technique was widely adopted.

In 2004, Losken, et al reported on their experience with endoscopic-assisted harvest of latissimus dorsi muscles for reconstructing partial mastectomy defects². The authors sought to evaluate the risks and benefits associated with immediate versus delayed muscle flap transfers. Thirty-nine cancer patients with an average follow up of 3.67 years were included in this review. Donor site complications occurred in 12 patients and included: seromas (7), hypertrophic scarring (1), skin loss (1) and wound dehiscence (1). One patient experienced postoperative lymphedema and another had a persistent sinus

tract requiring excision with pectoralis muscle flap reconstruction. To reduce the risk of cancer recurrence following mastectomy procedures, the authors recommended confirmation of negative margins prior to latissimus dorsi muscle transfer.

In 1998, Masuoka, et al reported on 7 patients who underwent breast reconstruction surgery with the latissimus dorsi muscle flap combined with a saline implant using an endoscopic approach for muscle harvest⁶. The authors employed the use of a modified endoscopic technique performed through a larger incision due to former surgery. This approach proved easier than standard endoscopy because the procedures were performed under direct visualization. As such, this methodology maximized acquisition of optical space, a limitation of subcutaneous endoscopic surgery. The authors concluded that harvesting a latissimus dorsi muscle flap using an endoscope was a useful method to avoid additional scarring.

Free Latissimus Dorsi Flap Literature

In a 1990 review conducted by Furnas, 18 patients underwent scalp reconstructions of complicated scalp wounds with 21 free flaps: 11 from the latissimus dorsi, 3 scalp transfers between identical twins, 3 groin, 1 combined latissimus dorsi and serratus anterior, 2 serratus anterior, and 1 omentum³. All of the flaps survived with follow up ranging from 3 weeks to 7 years. The latissimus dorsi was shown to be their first choice for free flap reconstruction of scalp wounds because of its large size, predictable blood supply, ease of harvesting, and provision of excellent vascularity to compromised beds.

Many other additional studies since then have confirmed the popular use of the latissimus dorsi free flap for scalp reconstruction. The complication rate is low and cosmesis was satisfactory¹⁰.

In 1997, Cho, et al reported on 10 patients with lower extremity reconstructive procedures which utilized free latissimus dorsi muscle flaps⁷. Muscle harvest was accomplished endoscopically with a 5-6 cm incision. The largest harvested muscle was 15 x 25 cm. An average time of 2-3 hours was required for muscle flap harvest. No donor site complications such as hematomas or seromas were observed. The patients were satisfied with the short donor site scars and reported decreased postoperative pain. The authors concluded that endoscopic harvesting techniques had several limitations. Specifically, they opined that the key to successful endoscopic free flap transfer is operative dexterity, experience and access to proper instrumentation. They also emphasized the need for good visualization and proper hemostasis to avoid complications.

3.3 Conclusion

Endoscopic approaches for either a pedicled or free latissimus dorsi muscle flap harvest have been successfully employed. However, there are a variety of problems with the endoscopic approach⁷. One problem is that the optical window is very tight, preventing visualization of the appropriate anatomic structures that allow for safe harvest.

Instrumentation presents a second issue; endoscopic instruments are long and unwieldy, making precise dissection and hemostatic management challenging, particularly in the context of difficult retraction and poor visualization. These impediments have impaired widespread adoption of minimally invasive techniques for muscle harvest procedures.

In this study, we hypothesize that the *da Vinci*® robotic surgical system may offer distinct advantages for enabling surgical harvest of the latissimus dorsi flap through small incisions. The advantages of the robotic platform are precision and visualization which are anticipated to address many of the reported issues such as bleeding and flap necrosis by allowing the surgeon to better monitor and control their surgical technique. By creating an optical window with the use of insufflation, camera and instruments can be comfortably positioned within tight spaces to operate using very precise movements. Because incisions are limited to three ports, the largest of which is 1.2 cm, this technology is well suited to minimally invasive muscle harvest, and solves some of the challenges that endoscopic flap harvest presents.

In summary, a variety of endoscopic surgical techniques have been proposed over the past 15 years to harvest latissimus dorsi muscle flaps but none have achieved widespread adoption despite a strong patient benefit. It is hoped that robotic-assisted latissimus dorsi flap procedures will help overcome some of the limitations inherent in the current endoscopic approaches. This study seeks to evaluate the safety and feasibility of this robotic-assisted approach and will evaluate donor site complications and flap survival in patients requiring latissimus dorsi muscle harvest for subsequent breast, scalp, upper extremity, and lower extremity reconstructive procedures.

4 PRIOR INVESTIGATIONS

Robotic-assisted latissimus dorsi muscle flap harvests have been completed using the *da Vinci*® robotic surgical system in 10 cadavers and 15 clinical patients. All procedures were completed by the Principal Investigator for this proposed study. A summary of the procedures completed by Jesse Selber, MD, is provided below.

4.1 Cadaver Evaluation

Ten robotic latissimus dorsi muscle harvests were performed in 10 cadavers from 2009 to 2010⁸. All dissections were performed by the study's principal investigator, Jesse Selber,

MD, using the *da Vinci*® robotic surgical system. All 10 latissimus dorsi muscles were harvested successfully in their entirety. The goal of these cadaveric studies was to develop and refine the port placement, workflow and operative technique. Dr. Selber concluded that the robotic-assisted endoscopic harvest technique was both feasible and reproducible.

4.2 Initial Clinical Experience

Following the cadaveric studies of 7 cases⁹, 15 patients underwent robotic-assisted harvest of the latissimus dorsi muscle at MD Anderson. The harvested muscles were used as free flaps for scalp reconstruction in 3 patients and as pedicled flaps for breast reconstruction in 12 patients. The procedures were completed using a total of 3 ports. The latissimus dorsi muscles were fully dissected with robotic instruments along the superficial and deep surfaces of the muscle with good hemostatic control and then disinserted along the inferior and posterior borders for delivery into the axilla. At this stage, the axillary incision was then re-opened and the muscle delivered through the short incision. The robot was then undocked. An endoscope was introduced to confirm adequate hemostasis and drains were positioned in the donor site, brought out of the port sites, and sutured into place. The reconstructive portion of the procedure then commenced manually.

Fifteen muscle flaps were harvested in 15 patients without converting to an open procedure. Both free flaps were successfully transferred. All pedicled flaps resulted in successful breast reconstructions. Robotic harvest times averaged 1 hour and 51 minutes. Flap harvest complications included a single instance of transient and partial contralateral radial nerve palsy resulting from inadequate axillary support in the context of lateral decubitus positioning. This patient had full recovery within 2 weeks. All patients reported moderate back/flank discomfort during hospitalization and minimal to no discomfort during the first follow up visit at 1 week post discharge. One patient required occupational therapy of 2 weeks duration postoperatively. There were no donor site hematomas or seromas. There were no reports of injuries to the overlying skin, and there are no records of any skin injuries or delayed wound healing in clinic notes.

Dr. Selber concluded that the robotic-assisted technique offered technical advantages over endoscopic harvest and cosmetic advantages over the open technique. Additionally, this case series demonstrated that robotic-assisted harvest is useful for both pedicled and free flap reconstructive procedures.

5 INTENDED USE

The *da Vinci*® robotic surgical system is intended to assist in the accurate control of Intuitive Surgical endoscopic instruments during latissimus dorsi muscle flap harvest procedures in patients scheduled to undergo subsequent reconstruction procedures which require a muscle only flap (free or pedicled). In this study the free flaps will be used for scalp, upper extremity, and lower extremity reconstruction and pedicled flaps will be used for breast reconstruction. The *da Vinci*® robotic surgical system is intended for use by trained physicians in an operating room environment in accordance with the system User Manual (Appendix I) and this clinical protocol.

6 STUDY DEVICE

6.1 Description

The *da Vinci*® robotic surgical system is a computer assisted device designed to facilitate complex surgery using a minimally invasive approach. The system consists of the following 3 main components: 1) Surgeon Console; 2) Patient Cart; and, 3) Vision System Cart. These components are described below and depicted in Figure 1.

Surgeon Console: is the control center for the system. While seated at the surgeon console (outside of the sterile field) and as observed through the console's stereo viewer, the surgeon controls critical aspects of the surgical procedures, including movement of the endoscopic instruments and endoscope within the operative field. Instrument and camera movements are controlled by the surgeon through the use of 2 hand operated controllers residing in the console and foot pedals at the console's base. These features allow the surgeon to be as dexterous as in "open" surgery, while operating in a minimally invasive environment. The surgeon at the console also has the option to change the surgical view from full screen mode to a multi-image mode, which displays the 3-dimensional (3-D) image of the operative field.

Patient-Side Cart: is the operative component of the surgical system within the sterile field. Its primary function is to support the EndoWrist® instrument arms and camera arm during surgical procedures. EndoWrist instruments are designed to provide surgeons with natural dexterity and a greater range of motion than the human hand. This allows for greater precision when operating in a minimally invasive environment. EndoWrist instruments are designed to support rapid and precise suturing, dissection and tissue manipulation in surgical procedures.

Vision System Cart: houses the system's imaging processing equipment and is operated by a person outside of the sterile field during surgery. The cart provides space for an

optional touch screen monitor as well as ancillary surgical equipment. The cart consists of a stereo endoscope, endoscopic camera and various accessories including a light source and light guides. The Insite Vision System provides 2 independent images that are relayed to the viewer located in the surgeon console, where they are used to form a 3D image (or alternatively 2D) of the surgical field for the surgeon's reference.

Figure 1: Overview of the *da Vinci*[®] System (Console, Patient-side Cart and Vision System)



6.2 Device Requirements

The *da Vinci*[®] robotic surgical system is available commercially for a variety of cleared indications. MD Anderson currently has the *da Vinci*[®] Si system at their facility in use for transoral robotic surgery (TORS), prostatectomy, hysterectomy, thoracic procedures, and general surgeries. The existing *da Vinci*[®] Si system will be used in conjunction with standard commercially available *da Vinci*[®] instruments including: monopolar curved scissors, Maryland with bipolar, Cadiee grasping forceps, and 3D endoscopes.

7 STUDY OBJECTIVES

The objective of this study is to evaluate the safety and feasibility of the *da Vinci*[®] robotic surgical system in 15 subjects undergoing latissimus dorsi muscle flap harvest procedures in conjunction with breast, scalp, upper extremity, and lower extremity reconstruction procedures. Donor site complications and flap viability will be assessed intraoperatively and through 6 months post-procedure, and length of stay and analgesic use as an inpatient will be compared to historical controls of the open approach.

8 STUDY ENDPOINTS

8.1 Primary Safety Endpoint:

The primary safety endpoint is muscle flap failure.

8.2 Primary Efficacy Endpoint:

Latissimus dorsi muscle flap viability evaluated by clinical assessment and doppler examination at the end of the muscle harvest portion of the surgical procedure.

8.3 Secondary Endpoints:

1. Evaluation of donor site complications through 6 months post-procedure.
2. If the flap is for external use, interval viability with a Doppler proximally and distally will be checked at 3 months post-procedure.
3. If the flap is for pedicled, internal use over an implant, no additional evaluation will be possible unless planned or unplanned reoperation exposes the muscle, at which time a Doppler evaluation would be undertaken.
4. Conversion rate (i.e., completion of the latissimus dorsi harvest procedure with the *da Vinci*® *Robotic Surgical system* without converting to an open procedure).
5. The validated QuickDASH questionnaire to evaluate postoperative shoulder function as compared to preoperative QuickDASH shoulder function.
6. Postoperative pain assessed by validated visual analog scale (VAS).
7. Physical therapy assessment of range of motion and strength of the affected shoulder using the validated American Shoulder and Elbow Surgeons (ASES) assessment tool.
8. Length of stay and analgesic use to be compared to historical controls of the open procedure.

9 METHODS

9.1 Study Design

This is a prospective, non-randomized, single-arm study of the *da Vinci*® robotic surgical system in subjects undergoing latissimus dorsi muscle flap harvest procedures in conjunction with breast, scalp, upper extremity and lower extremity reconstructive procedures. This study will be conducted at MD Anderson in Houston, Texas. Muscle flap failure and donor site complications will be assessed through 6 months post-procedure. Flap viability will be assessed following completion of the robotic-assisted harvest procedure. Flap viability is defined as having a pink, non-congested appearance and an audible arterial and venous Doppler signal. Additional assessments of viability will include bleeding at the distal extremes of the muscle when cut sharply, and an audible Doppler signal detected in the distal third of the muscle.

9.2 Study Duration

This study is expected to commence in the first quarter of 2015. Enrollment of all subjects is expected to be completed in the second quarter of 2017. Six month clinical follow up is expected to be completed within the fourth quarter of 2017.

9.3 Number of Subjects

Fifteen subjects \geq 18 years of age, meeting all inclusion and exclusion criteria will be enrolled. Subjects will undergo robotic-assisted latissimus dorsi muscle harvest in conjunction with a standard surgical breast, scalp, upper extremity, or lower extremity reconstructive procedure requiring free or pedicled flaps.

9.4 Eligibility Criteria

9.4.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for enrollment in this trial:

- 1) The subject must be equal to or greater than 18 years of age.
- 2) The subject must be willing and able to provide informed consent.
- 3) The subject is willing and able to comply with the study protocol.
- 4) The subject is undergoing one of the following reconstructive procedures that requires latissimus dorsi muscle harvest:
 - a. Post-mastectomy breast reconstruction procedure (either nipple or skin sparing) in which a female subject needs additional muscle coverage over an implant, but does not need additional skin (i.e., patient is a candidate for a pedicled latissimus dorsi muscle flap procedure);
 - b. Scalp reconstruction procedure in which the subject needs a free latissimus dorsi muscle flap for wound coverage;
 - c. Upper extremity reconstruction in which the subject needs a free latissimus dorsi muscle flap for wound coverage; or,
 - d. Lower extremity reconstruction in which the subject needs a free latissimus dorsi muscle flap for wound coverage.
- 5) The subject agrees to follow up examinations out to 6 months post-treatment.

9.4.2 Exclusion Criteria

Subjects will be excluded from this trial if any of the following criteria are met:

- 1) The subject has a BMI > 35.
- 2) The subject has a history of significant bleeding disorders.
- 3) The subject is diabetic.

- 4) The subject is known or suspected to be pregnant or lactating.
- 5) The subject has a history of peripheral vascular disease.
- 6) The subject is a current smoker (has smoked within 4 weeks prior to surgery).
- 7) The subject has had prior back or axillary surgeries which could compromise the blood supply of the flap.

9.5 Withdrawal of Subjects

Subjects may voluntarily withdraw their participation from the study at any time. Investigators may withdraw a subject from the study as deemed appropriate per safety measures and/or if the subject's medical condition contraindicates further study participation. All subjects withdrawn from the study will undergo a final study visit consisting of a safety evaluation.

9.6 Evaluation Tests

The disabilities of the arm, shoulder and hand (QuickDASH) questionnaire is a self-administered outcome instrument developed as a measure of self-rated upper extremity disabilities and symptoms (Appendix E). The QuickDASH consists of 11 items scored 0 (no difficulty) to 5 (unable/extreme) with 8 optional occupational questions. It has been validated for longitudinal construct and been rated effective as a post-surgery measurement tool.¹¹

The validity of VAS has been well studied for eliciting reproducible pain assessments^{12,13,14}. In pain research VAS are considered 'the gold standard' for pain assessments. Subjects report their level of pain through the scale. A copy of the VAS is located in Appendix F.

The functional evaluation of the shoulder uses the American Shoulder and Elbow Surgeons (ASES) method which is a standardized form for shoulder assessment¹⁷. The physical therapy assessment section includes range of motion and strength. While a comparison is regularly made between the operated versus non-operated shoulder, for this study, the subject will have an initial baseline test done preoperatively to compare with the postoperative evaluation. The measurement of active and passive range of motion and the manual muscle-testing will be performed on all subjects by a member of the Physical Therapy staff. Shoulder mobility is expressed in degrees with abduction, adduction, intra-rotation and extra-rotation measured both actively and passively. A sample of the range of motion and strength forms are located in Appendix G.

10 RISK-BENEFIT ASSESSMENT

10.1 Risks

As part of the robotic-assisted muscle harvest procedure the thoracodorsal nerve may sometimes be intentionally sacrificed resulting in a known risk of impaired range of motion (internal rotation and abduction of the arm <90 degrees). Pneumothorax from unintentional entrance into the pleural space is also a potential risk but very rarely occurs in either open or endoscopic muscle harvest^{1,5,16}. Clinically detectable postoperative pneumothorax will be managed in consultation with the thoracic surgery service. Management will include chest tube placement and monitoring with serial upright and lateral chest x-rays. Pneumothorax has not been present in the over 30 clinical cases thus far. In order to detect unintended pneumothorax, the muscle donor site cavity will be subjected to positive pressure ventilation by the anesthesiologist to insure that no small pneumothorax has occurred. In the event of a pneumothorax detected intraoperatively, the anesthesiologist will be made aware immediately and an intraoperative consult to a thoracic surgeon will immediately result. If a chest tube or catheter is deemed necessary, it will be placed at that time under direct vision by a board certified thoracic surgeon.

In addition, there are other standard risks associated with any latissimus dorsi harvest procedure independent of the method of harvest. These include: 1) postoperative pain; 2) bleeding which may require transfusion; 3) infection at the donor or transfer site; 4) numbness or tingling; 5) thrombosis of the pedicle; 6) scarring, wound dehiscence, or delayed wound healing at the incision site; 7) partial or total flap necrosis or loss; 8) pulmonary embolism; 9) inflammatory syndrome; and, 10) swelling, seroma or hematoma at the donor site. These will all be managed according to standard hospital procedures.

Potential risks that are unique to endoscopic harvest include subcutaneous emphysema as a result of insufflation, and bleeding which cannot be managed endoscopically. Subcutaneous emphysema with CO₂ requires no additional postoperative management as it resolves quickly and is not in a position to impinge on the airway^{18,15}. Bleeding that cannot be managed endoscopically may be controlled with direct external pressure and conversion to open techniques, when necessary. This has not occurred in any of the robotic harvests to date, and it is believed that hemostasis will be easier to maintain and regain with robotic instruments than with standard endoscopic techniques.

Additional risks presented by use of the *da Vinci*® robotic surgical system other than those listed above include the possibility of a device malfunction which may require a conversion to an open procedure. If the system is unavailable for use or other clinical factors proscribe system use, the physician may convert to a standard open surgical procedure.

There are also small additional risks associated with the patient being under anesthesia for a longer period of time which will be required given the slightly longer length of time expected for robotic-assisted procedures when compared with open techniques. However, early clinical work has already shown lower operative times with the *da Vinci*® robotic surgical system than previously reported endoscopic harvests.

The above referenced risks will be mitigated in two ways. First, Dr. Selber and Dr. Clemens, both experienced plastic and reconstructive surgeons, who have been extensively trained on the *da Vinci*® robotic surgical system, will be the only two surgeons performing procedures under this study protocol.

10.2 Benefits

There is no proven benefit related to use of the *da Vinci*® robotic surgical system for latissimus dorsi muscle harvest surgical procedures. It is hoped that the investigational device will permit a simpler, minimally invasive harvest technique with smaller incisions, decreased postoperative time and a quicker return to normal activities. However, the device has not yet been studied to demonstrate its utility in this regard. Subjects may benefit from the additional clinical monitoring and follow up evaluations required by this study protocol.

11 STUDY PROCEDURES

11.1 Subject Screening and Baseline Evaluation (Visit 1)

Subjects will be recruited for this study from MD Anderson. All subjects requiring latissimus dorsi muscle harvest procedures in conjunction with breast, scalp, upper extremity, or lower extremity reconstruction procedures will be screened for eligibility. The Investigator or a member of the research team will review the subject's medical history for eligibility and inclusion into the study. If all inclusion criteria are met and no exclusion criteria are present, the Investigator will inform the subject about the purpose of the study and will obtain written informed consent. The background of the proposed study along with the benefits and risks will be explained to the subject and questions will be answered. The subject must sign an informed consent that has been approved by the MD Anderson Institutional Review Board (IRB). Failure to provide informed consent renders the subject ineligible for the study.

The Investigator or a member of the research team will record the subjects' medical history and demographic information on a case report form tool. Protocol specific data and adverse events will be entered into the MD Anderson REDCap™ database. The first assessment of adverse events will take place in the operating suite at the time of surgery

and will continue for 6 months following surgery. The medical history will include information about previous treatments to further ensure compliance with the inclusion and exclusion parameters. The Investigator will conduct a medical history review and a physical exam. A pre-anesthesia appointment will also be coordinated. The Investigator or a member of the research team and subject will also complete a QuickDASH questionnaire. The subject will also undergo a physical therapy assessment to test the range of motion and strength of the shoulder to be used as a baseline postoperatively. As standard of care for patients undergoing these procedures, a pregnancy test will be ordered by the Anesthesia Department for appropriate female patients. This visit may be completed within 30 days prior to treatment/surgery.

11.2 Treatment (Visit 2)

The subject will be taken to the operating room for surgery under general anesthesia with no muscle paralysis. The robotic-assisted latissimus dorsi harvest procedure will be performed as described in the protocol and will be videoed and/or photographed. Medications used, port placements, procedural details, adverse events and device details will be documented on the CRFs (Appendix H). Muscle flap viability will be assessed by clinical examination and doppler assessment prior to the reconstruction procedure. Such assessments will be documented in the CRFs (Appendix H) prior to the standard surgical breast, scalp, upper extremity, or lower extremity reconstruction procedure.

11.3 Follow Up Evaluations (Visits 3-6)

Patients will be seen in the office for a visit within 0-2 weeks and then within 2-4 weeks after the surgical procedure. The next visit will be between 1-3 months after the procedure. The final visit will be between 3-6 months after the procedure. At these postoperative visits, incisions and drain sites will be checked and donor sites will be evaluated for adverse events. Additionally, pain assessments, the QuickDASH questionnaires, and the range of motion and strength tests will be administered. Drains will be removed as appropriate at approximately 2 to 3 weeks after the procedure.

11.4 Schedule of Events

The protocol does not require any clinic visits other than those that are standard of care for patients undergoing robotic-assisted harvest of the latissimus dorsi muscles.

Study Events	Screening & Baseline Evaluation (Visit 1) ¹	Procedure / Treatment (Visit 2)	Post Op Follow Up (Visits 3-6) ^{2,3}
Eligibility Screening	X		
Secure Informed Consent	X		
Medical History and Physical Exam (to include BMI)	X		

Pre-Anesthesia Appointment (to include Urine Pregnancy Test - if appropriate per Anesthesia)	X		
Baseline QuickDASH Questionnaire	X		
Baseline Physical Therapy Assessment (to include testing range of motion and strength of the shoulder)	X		
Robotic-Assisted Latissimus Dorsi Flap Harvest Procedure & Non-robotic Reconstruction Procedure		X	
Flap Viability Assessment via Clinical and Doppler Examinations		X	
Adverse Event Assessment		X	X
Postoperative QuickDASH Questionnaire			X
Postoperative Physical Therapy Assessment (to include testing of range of motion and strength of the shoulder)			X
Patient Questionnaire of Pain via VAS			X
Drains Removed			X

¹ Occurs within 30 days prior to surgery.

² Visit 3 (occurs between 0-2 weeks), Visit 4 (occurs between 2-4 weeks), Visit 5 (occurs between 1-3 months)

³ Final Visit (occurs between 3-6 months)

12 STATISTICAL ANALYSIS PLAN

This is a prospective, non-randomized, single-arm study designed to assess the safety and feasibility of the *da Vinci*® robotic surgical system in latissimus dorsi muscle flap harvest procedures. A maximum of 15 subjects requiring latissimus dorsi flap harvest procedures in conjunction with breast, scalp, upper extremity, or lower extremity reconstruction procedures will be enrolled at MD Anderson in Houston, Texas.

The muscle flap failure will be monitored using the Bayesian stopping boundaries calculated based on beta-binomial distribution. We will consider that the *da Vinci*® robotic surgical system is promising in latissimus dorsi flap harvest if the muscle flap failure rate is below 10%. With a sample size of 15 patients, the probability of observing at least one muscle flap failure is 79.4%. The prior probability of muscle flap failure is modeled by beta distribution (Beta (0.1, 0.9)). Denoting the probability of muscle flap failure by θ , and it is compared to fixed target of 10%. The following decision criterion will be applied: Stop if $\text{Prob}\{\theta > 0.10 \mid \text{data}\} > 0.75$.

Patients will be monitored by a cohort size of 5 according to the following stopping boundaries for muscle flap failure. The patient enrollment will be halted for this safety monitoring because the status of muscle flap failure can be obtained right after surgery.

Number of patients evaluated	Stop if \geq muscle flap failure observed
5	2-5
10	2-10
15	Always stop with this many patients

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True DLT Rate	Prob (stop the trial early)
0	0
0.05	0.0861
0.10	0.2639
0.15	0.4557
0.20	0.6242
0.25	0.7560
0.30	0.8507

The above stopping boundaries and operating characteristics are calculated using MultcLean (v.2.1.0) design software downloaded from <http://biostatistics.mdanderson.org/SoftwareDownload>.

The muscle flap failure rate and its 95% confidence interval (CI) will be calculated using the exact method. Other outcome data to be collected will include: pain assessment using a validated VAS, QuickDASH score, and physical therapy assessment.

Patient information including age, gender, body mass index (BMI), medical history, history of radiation, history of smoking, defect characteristics (such as "partial breast, scalp, upper extremity, or lower extremity"), donor site morbidity, and functional deficits will be summarized. The rate of donor site morbidity and their 95% confidence interval will be reported.

Operative Variables: Length of surgery, type of defect, size of defect, type of reconstruction, length of incision used, length of robotic portion of the procedure, robotic instrumentation used, port placement. This information will be documented by the OR staff during surgery, and collected by the research team after surgery on standardized CRFs.

Outcome Variables: Length of stay, pain medication requirements, postoperative complications (such as seroma, wound dehiscence, delayed wound healing, or flap loss), length of time drains are required in donor site, and postoperative return to normal function, as well as, any residual functional deficits, defined as a subjective decrease in strength, range of motion or restriction in activities of daily living will be assessed at

between week 0-2, and between week 2-4 after the procedure. The subject will then have an evaluation at 3 months after the procedure. The subject's last follow up visit will occur 6 months post-procedure.

The safety of the robotic-assisted latissimus dorsi procedure will also be evaluated based on adverse events related to the donor site through 6 months post-procedure. Acute complications include but are not limited to: seroma; hematoma; overlying skin damage; and, injury to the muscle or vascular pedicle. All adverse events will be further categorized and documented according to section 13 of this clinical protocol.

The feasibility of the procedure will be evaluated based on the number of successfully completed robotic-assisted latissimus dorsi harvest procedures among the total attempted procedures. Any procedure that is abandoned or converted to an open surgical or endoscopic technique after being initiated with the *da Vinci*® robotic surgical system will be considered a failed *da Vinci*® procedure. The rate of successfully completed harvest procedure will be calculated along with its 95% CI.

The efficacy of the procedure will be determined based on the rate of subjects who demonstrate a viable flap assessed by clinical and doppler examinations at the end of the harvest procedure. It is recognized that the overall success of the surgery from the patient's and surgeon's perspectives includes the success of the harvest and reconstruction procedures. However, the objective of this investigational protocol is to evaluate the robotic-assisted muscle harvest technique only. As such, flap viability prior to reconstruction is the most relevant outcome for this study. Additional secondary assessments will include: long term survival of the flap and flap necrosis at the postoperative visits. These assessments will not be employed to adjudicate the primary efficacy endpoint.

12.1 Study Power and Sample Size

The specific sample size for this investigation is not based on the testing of a specific hypothesis with a degree of power to detect a difference. As such, a maximum of 15 subjects will be enrolled in the study with the intent of establishing baseline outcomes for this procedure.

12.2 Performance Analysis Cohorts

12.2.1 Intent to Treat Analysis

All subjects who enroll in the study and are treated with the *da Vinci*® robotic surgical system will be included in the Intent-to-Treat analysis. Subjects who terminate prior to completing the study will have their score set to their last available value for the visits after

they terminated from the study with missing data. No other special data handling algorithms will be used for imputing missing data.

12.2.2 Per Protocol Analysis

All subjects who complete the study according to the protocol will be included in the Per-Protocol analysis. No special data handling algorithms will be used for imputing missing data for subjects included in the Per-Protocol analysis.

12.3 Endpoint Analysis and Reporting of Results

All statistical analysis will be performed using SAS Version 9.3 (SAS Institute Inc., Cary, NC).

13 ADVERSE EVENT REPORTING

Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. Note: This also includes events related to the study device and/or the study procedure. The U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, will be used to grade adverse events.

All AEs related to the surgery that are observed by the Investigator or staff during a procedure, physical or laboratory examination, or mentioned by the subject either spontaneously or upon questioning will be recorded in REDCap™. Information pertaining to the recorded AE will be reviewed and verified by the IRB or its designated representative. The Investigator is responsible for assessing the severity of the AE, the causal relationship between any events and the clinical study procedure, activities or device. Additionally, the Investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution. The following categories of adverse event severity are to be used by the Investigator:

- Mild: Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no clinical sequelae;
- Moderate: Interferes with the subject's usual activity; and,
- Severe: Any fatal or immediately life-threatening clinical experience that requires a subject to be hospitalized, or hospitalization is unduly prolonged because of a

potential disability or danger to life or because an intervention has been necessitated. This includes any permanently disabling event.

The following categories of AE relatedness to the study device and procedure will be used by the Investigator:

- Possibly Related – may be related to study agent/device.
- Probably Related – is likely related to study agent/device.
- Definitely Related – is clearly related to study agent/device.

Adverse Device Effect (ADE)

An Adverse Device Effect (ADE) is defined as an adverse event related to the use of an investigational medical device. Note: This definition includes adverse events resulting from insufficient or inadequate instructions of use, deployment, installation, operation or any deficiency of the investigational medical device.

Serious Adverse Event (SAE)

The following events (including laboratory results and outcome events) will be considered SAEs and must immediately (within 1 working day [24 hours] from the time the research team becomes aware of the event) be reported to the IRB as set forth in the MD Anderson AE Policy (Chapter 15 of the Human Subject Research Manual). These events must be reported whether or not the Investigator believes they are related to the study procedures or the device.

A serious adverse event is any adverse event that:

- results in death;
- is life-threatening, (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant incapacity or substantial disruption of a person's ability to conduct normal life functions;
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Serious Adverse Device Effect (SADE)

An adverse device effect that has resulted in any of the consequences of a serious adverse event. This includes SADE's which by its nature, incidence, severity or outcome

has not been identified for the investigational study device. SADE's must be reported to Intuitive Surgical within 24 hours by telephone, fax and/or email.

Unanticipated Serious Adverse Device Effect (USADE)

This includes SADE's which by its nature, incidence, severity or outcome has not been identified for the investigational study device. USADE's must be reported to the IRB in accordance with Chapter 15 of MD Anderson's IRB Policy on Adverse Event Reporting and Management.

Unanticipated Adverse Device Effect (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect or problem, was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

Because no investigational drugs or regimens are used in this study, only Unanticipated Adverse Device Effects will be reported to the IRB and the IND Office. Events that are related to the neoadjuvant therapy or surgery will not be reported or recorded in the case report form.

All UADE will be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices".

Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and IRB. Unanticipated Adverse Device Effects will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 812.150.

It is the responsibility of the PI and the research team to ensure unanticipated adverse device effects are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the MD Anderson guidelines, and Institutional Review Board policy.

Device failure

Device failures which occur at the time of participant evaluation and which may prevent a participant from receiving therapy on trial will be kept on a log and will be reported as part of the annual report. Device failures at this point are not expected to affect patient safety, as participants may still receive appropriate therapy as determined by their attending physician.

14 GOOD CLINICAL PRACTICES (“GCP”)

14.1 Institutional Review Board (IRB) Approval

Prior to study initiation, this protocol, the informed consent and any advertisements for subject recruitment must be submitted to the IRB for written approval. The IRB’s written notification of approval will be provided to the MD Anderson IND Office prior to study commencement. Any changes to the protocol that may increase study risks or present new risks to the subject or may adversely affect the outcome of the study must be approved in writing by the MD Anderson IND Office and the site IRB before the change is made.

14.2 Informed Consent

Subjects must provide informed consent in writing after having adequate time to consider their participation in the study pursuant to the Declaration of Helsinki requirements and local / US regulations. Consent must be obtained prior to any protocol-related procedures that are not part of the subject’s standard care. Written documentation of consent must be provided on the signature page in addition to a note in the study records indicating the date that consent was obtained. The subject or his/her legal representative should receive a signed copy of the consent form according to international GCP guidelines.

14.3 Subject Confidentiality

All information concerning subjects or their participation in this trial will be considered confidential. Only authorized personnel and designated consultants will have access to these confidential files. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this trial. Enrolled subjects will be assigned a unique identifier that will be used to maintain confidentiality of subjects’ medical information. Subject names and other protected health information will not be captured on the case report forms.

14.4 Data Collection

The Case Report Form (CRF) is the primary data collection instrument for the study. REDCap™ will be used as the electronic case report form. Primary data collection based on source documented hospital chart reviews will be performed clearly and accurately by the site personnel on the CRF. All missing data will be explained. If the item is not

applicable to the individual case, “N/A” will be written in the field. All entries will be printed legibly in black ink. To correct an error that has been made, a single line will be drawn straight across the incorrect entry and the correct data will be entered above it. All changes will be initialed and dated. A copy of the completed Case Report Forms will remain on site at the participating institution.

Study data will be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at MD Anderson. [ref] REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. In the case of multi-center studies REDCap uses Data Access Groups (DAGs) to ensure that personnel at each institution are blinded to the data from other institutions. REDCap (<https://redcap.mdanderson.org>) is hosted on a secure server by MD Anderson Cancer Center's Department of Research Information Systems & Technology Services. REDCap has undergone a Governance Risk & Compliance Assessment (05/14/14) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and UTMDACC Institutional Policy #ADM0335. Those having access to the data file include the study PI and research team personnel. All protected health information (PHI) will be removed from the data when it is exported from REDCap for analysis. All dates for a given patient will be shifted by a randomly generated number between 0 and 364, thus preserving the distance between dates. Dates for each patient will be shifted by a different randomly generated number. Following publication study data will be archived in REDCap.

14.5 Data Monitoring and Quality Control

All collected data will be verified for accuracy with source documents including, but not limited to, medical records, office/clinic notes, procedure reports, laboratory results, physician and nursing progress notes. Verification and quality of data, monitoring of clinical study progress and Investigator compliance with the approved protocol will be conducted by the MD Anderson IND Office or a designated representative.

The MD Anderson IND Office or its designated representative will be allowed to visit the clinical site and have direct access to all study records throughout the duration of the study. The monitor will review all source data and compare them to the data documented in the case report forms, in addition to performing a review of the Regulatory Binder, and conducting device accountability. The Investigator and/or institution will provide direct

access to source data/documents for trial-related monitoring, audits, IRB review and regulatory inspection.

14.6 Record Retention

The Study Sponsor and Investigator will retain essential documents relating to this clinical study for at least two (2) years after study completion or two (2) years post marketing approval, whichever is longer. Records may be retained for a longer period as agreed to by the Study Sponsor and Investigator.

14.7 Protocol Monitoring Plan

This is a single-arm study and, therefore, does not require MD Anderson's Data Safety Monitoring Board (DSMB) review. This study will be monitored by the MD Anderson IND Office and the Principal Investigator. A protocol-specific monitoring plan will be followed.

The trial will be stopped if flap failures are observed in 2 of the first 5 patients treated. The trial will also be stopped if flap failures are observed in 2 of the second set of 5 patients treated. Flap failure is defined as irreversible arterial and venous thrombosis detected by implantable or surface doppler signal within 72 hours after surgery. Notice will be provided to the Principal Investigator, the IRB, and the FDA should early termination of the trial be recommended. The trial will not restart until a thorough risk analysis has been completed and the FDA and IRB provide their written approval to restart the study.

15 Protocol Deviations

Dr. Selber and Dr. Clemens will not deviate from the protocol except in medical emergencies. If a medical emergency occurs, prior approval will not be required but the IRB must be notified of the deviation in accordance with Chapter 25, Reporting Requirements and Timeframes of MD Anderson's IRB Policy on Reporting Protocol Deviations.

16 Device Accountability

The *da Vinci*® robotic surgical system and the corresponding instruments that will be used in this study have been FDA cleared for a variety of surgical indications. Dr. Selber and Dr. Clemens will use the *da Vinci*® robotic surgical system and instruments that are currently in use at MD Anderson for other cleared clinical indications. MD Anderson will ensure that the Investigator and clinical site personnel are aware they must report any device malfunction related to this study to Intuitive Surgical within 24 hours. In addition, clinical site personnel must complete the Device Performance Issue-Malfunction case report form (Appendix H).

17 SPONSOR RESPONSIBILITIES

As the Study Sponsor, MD Anderson is committed to the following activities pursuant to international GCP guidelines:

- 1) Securing the necessary IRB and government approvals for this protocol;
- 2) Obtaining all required approvals prior to device usage under this investigational protocol;
- 3) Selecting a qualified investigator;
- 4) Ensuring proper investigator training;
- 5) Ensuring proper clinical site monitoring;
- 6) Ensuring that the IRB is informed of any significant new information about the study;
- 7) Maintaining accurate and complete study records and submitting required reports;
- 8) Obtaining a signed clinical trial / investigator agreement;
- 9) Providing case report forms and ensuring that the completed forms match source documentation;
- 10) Ensuring protocol compliance; and
- 11) Ensuring proper reporting of all AEs.

18 INVESTIGATOR RESPONSIBILITIES

Dr. Selber will sign a Clinical Trial Agreement affirming that he will adhere to the following activities pursuant to international GCP guidelines:

- 1) Ensuring that enrolled subjects comply with the inclusion/exclusion criteria;
- 2) Obtaining written IRB approval prior to study initiation;
- 3) Obtaining written informed consent from each subject prior to enrollment;
- 4) Performing the study evaluations as described in this protocol;
- 5) Maintaining source documentation in the subject's medical files;
- 6) Completing case report forms corroborated by source documentation;
- 7) Submitting required reports to the Study Sponsor, IRB and regulatory authorities;
- 8) Complying with the study protocol and reporting any deviations in advance of their occurrence;
- 9) Maintaining study related records;
- 10) Maintaining accurate records related to device accountability; and
- 11) Ensuring proper reporting of all AEs.

19 STUDY MONITORING

The study monitor is a Clinical Research Monitor employed by the IND/IDE sponsor (MD Anderson). The Clinical Research Monitor will monitor the clinical study and report the

findings directly to the Medical Monitor and Vice President of Clinical Research. There will be one Clinical Research Monitor monitoring the study.

20 COMPENSATION IN THE EVENT OF INJURY

If the subject suffers injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to the subject's insurance provider or the subject in the ordinary manner. The subject will not be reimbursed for expenses or compensated financially by MD Anderson for this injury.

The subject may also contact the Chair of MD Anderson's IRB at 713-792-2933 with questions about study-related injuries. By signing the consent form, the subjects are not giving up any of their legal rights.

Certain tests, procedures, and/or drugs that the subject may receive as part of this study may be without cost to the subject because they are for research purposes only. However, the subject's insurance provider and/or the subject may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs, including hospitalization, nausea, vomiting, low blood cell counts, and dehydration. Standard medical care that the subjects receive under this research study will be billed to the subject's insurance provider and/or the subject in the ordinary manner. Before taking part in this study, the subject may ask about which parts of the research-related care may be provided without charge, which costs the subject's insurance provider may pay for, and which costs may be the subject's responsibility. The subject may ask that a financial counselor be made available to the subject to talk about the costs of this study.

There are no plans to compensate the subject for any patents or discoveries that may result from the subject's participation in this research.

The subject will receive no compensation for taking part in this study.

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