Protocol Title: Prospective Randomized Control Trial of Open versus Robotic REtrOmuscular Ventral Hernia repair [ORREO Trial]

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Background:
Due to the variety of hernia repair techniques and materials available, and the heterogeneity of the hernia patient population, there is no consensus standard of care for ventral hernia repair. The Rives-Stoppa retromuscular hernia repair is considered by many the standard by which all other techniques should be compared {Israelsson:2006gn}{Helgstrand:2013ev}. There is good long term data on this technique, with overall recurrence rate of 7.4% and wound complication rates of 9.3% (3). Unfortunately, many factors that lead to development of ventral and incisional hernias are also those that increase the risk of recurrence and wound morbidity. Obesity, COPD, DM, and tobacco abuse are particularly troublesome conditions that confer higher morbidity after abdominal wall reconstruction (AWR). While preoperative weight loss and smoking cessation are modifiable risk factors, many patients will not successfully lose weight, are not eligible for bariatric surgery, will not stop smoking, and are at risk for developing increasingly complex hernias or presenting with acute incarceration requiring urgent repair.

Since its initial description, laparoscopic ventral hernia repair (LVHR) was quickly adopted and has been shown to significantly decrease wound morbidity, with comparable recurrence rates (2) (3) (4). Though our preferred technique is an open retromuscular VHR (OVHR), laparoscopy remains an important technique for high risk patients. However, the hernia defect itself is typically not closed, which can result in pseudorecurrence and eventration of the mesh through the hernia defect, particularly with larger defects (5). Additionally, mesh placed in the intraperitoneal position has the potential to complicate subsequent abdominal operations, with incidence of unplanned enterotomy or bowel resection as high as 20% (6) (7).

The development of our robotic retromuscular ventral hernia repair (RRVHR) technique combines the benefits of the OVHR (reconstruction of native anatomy and a functional abdominal wall, placement of mesh in the retromuscular space) with those of LVHR (lower wound morbidity). Understandably, during the early development of a novel technique, we have been highly selective of our patients, typically selecting those we deem to have a high chance of a successful repair, and those with small to moderate defects as we refined the technical details of the operation. As our experience has increased and technique refined, we have been able to repair more complex patients with larger, more complex hernia defects. We

anticipate that these patients with the highest risk of wound morbidity will have the greatest clinical benefit from the robotic approach.

We describe a novel surgical technique, using new technology to duplicate the abdominal wall reconstruction achieved with OVHR in a minimally invasive fashion. While the feasibility of robotic VHR has been described, previous reports describe essentially a LVHR with intraperitoneal mesh placement utilizing the robot rather than a laparoscope. The only other report of a similar technique, and the inspiration of our development of RRVHR, is a transabdominal, retromuscular repair of umbilical hernia with plication of diastasis rectus described by Dr. Abdalla (8). The ability to duplicate a complete abdominal wall reconstruction with mesh reinforcement in high risk patients using a minimally invasive technique is a significant step forward in improving the outcomes in VHR. To our knowledge, we have the largest experience with this technique and the first reported outcomes data, which were presented at the World Hernia Congress, April 2015 (10).

Purpose:
The purpose of this study is to determine how the robotic retromuscular hernia repair compares to the open retromuscular hernia repair for large hernia defects in patients at higher risk of wound complications.

Hypothesis:
We hypothesize that the robotic retromuscular ventral hernia repair improves the clinical composite outcome, as compared to open retromuscular hernia repair, in high risk patients.

Primary Endpoints:

1. Composite Outcome (See full description below)
    a. Surgical Site Occurrence (excluding simple seroma)
    b. Surgical Site Infection
    c. Hospital Readmission
    d. Hernia Recurrence

Secondary Endpoints:

1. All Surgical Site Occurrences
2. Surgical Site Occurrences requiring procedural intervention
3. All Surgical Site Infections
4. Surgical Site Infections requiring procedural intervention
5. Length of Stay
6. Operative Time
7. Quality of Life
8. Cost

Composite Outcome:
In order to adequately power this study and provide a clinically relevant outcome measure, a composite outcome was designed to capture the outcomes that are considered clinically

significant. As such, simple seroma, which is very common, is excluded. Any seroma requiring procedural intervention will be included. Management of seroma or hematoma requiring intervention is discussed below under "Management of Complications." Other SSOs, such as skin dehiscence, cellulitis, hematoma or skin necrosis, are included as these are more likely to require some intervention, such as local wound care or drainage, or some additional cost, such as antibiotic therapy. Similarly, SSIs frequently require additional intervention and cost.

Study Design:
Prospective randomized control trial of robotic retromuscular ventral hernia repair versus open retromuscular ventral hernia repair in patients at high risk for adverse outcome. [Open versus Robotic REtrOmuscular Incisional hernia repair; ORREO trial]

Patient Selection:
All patients presenting to the Greenville Health System Hernia Center who meet the inclusion criteria will be considered for enrollment. Patients who agree to participate will be randomized to robotic retromuscular ventral hernia repair (group 1, RRVHR) or open retromuscular ventral hernia repair (group 2, OVHR). Randomization will occur in the office setting to allow appropriate scheduling of the case.

Participant Enrollment: 50 patients per study group (100 patients total)

Inclusion Criteria:

>18 years old
Ventral or incisional hernia measuring $\geq$7cm and $\leq$ 15cm
At least one of the following risk factors:
- BMI >30
- COPD
- DM
- Current smoker (within 1 month)

Exclusion Criteria:

Current abdominal or abdominal wall infection
Presence of ileostomy, colostomy, or ileal conduit
CDC wound class 3 or 4
Hernia defect < 7cm or >15cm
Pregnant women will be excluded from participating in this study.

Methods:
Prospective randomized control trial of robotic retromuscular ventral hernia repair versus open retromuscular ventral hernia repair in patients at high risk for adverse outcome. [Open versus Robotic REtrOmuscular Incisional hernia repair; ORREO trial]. Patients who agree to participate will be randomized to robotic retromuscular ventral hernia repair (group 1, RRVHR) or open retromuscular ventral hernia repair (group 2, OVHR). Randomization will be performed using the randomize function in the Redcap database.

Data Collection:
All patients will be entered prospectively into the Americas Hernia Society Quality Collaborative (AHSQC) database and followed prospectively. For data points that will be collected for trial purposes that are not contained within the AHSQC dataset, a Redcap database will be used.

Within the AHSQC, the following data is collected: Preoperative Patient Reported Outcomes via a validated, hernia specific quality of life questionnaire. Demographic data include age, sex, ethnicity, zip code, and insurance coverage. Patient characteristics include DM, COPD, HTN, immunosuppression, smoking status, hepatic disease, renal disease, antiplatelet or anticoagulant therapy, height/weight/BMI, history of previous hernia repair (including number of repairs, type of repair, type of mesh), history of previous abdominal wall infection, and functional status. Operative details include hernia width, height, presence of prior mesh, operative time, mesh selection, size of mesh placed, position of mesh placement, choice of mesh fixation, ability to close the midline fascia, technique for closure, use of component separation technique, and intraoperative complications. Hospital data will include LOS and any acute medical complications. Postoperative follow-up will occur at 2 weeks, 6 weeks, 6 months, 1 year, and 2 years. Patient Reported Outcomes will be collected at each of these post-operative visits. Cost data will be obtained from the Greenville Health System office of Business Intelligence after discharge from the index hospital stay, and include any readmission or additional procedural intervention.

Additional data not contained within the AHSQC, including patient account number, total operative time in minutes, total anesthesia time, and EBL, will be collected prospectively and recorded at the time of surgery completion. Operative time will be recorded as total anesthesia time and total operative time.

Operative Technique
Open Retromuscular Technique

- Midline laparotomy
- Adhesiolysis
- Removal of any prior mesh
- Defect measurement
- Bilateral retromuscular dissection, extending at least 5cm above and below the defect
- TAR (if necessary for posterior / anterior fascial closure OR for mesh coverage of more laterally oriented defect)
- Posterior sheath closure
- Dissected space measured
- Mesh placement (Vitamesh)
- Mesh fixation at minimum of 4 fixation points
- Anterior fascia closure using running, small-bite technique using slowly absorbable suture

- Skin closure with subcuticular fast-absorbing suture and surgical glue
- No drains will be placed

Robotic Retromuscular Ventral Hernia Repair

One of the following techniques, depending on location and technical feasibility.

Double-Dock Technique

- Three right (or left) lateral abdominal wall trocars
- Adhesiolysis and hernia reduction
- Removal of any prior intraperitoneal mesh
- Contralateral retromuscular dissection, extending 5cm above and below defect
- Contralateral transversus abdominis release with placement of right-sided trocars
- Mesh placement (Vitamesh)
- Intracororeal measurement of hernia defect and dissected space
- Mesh fixation at minimum of 4 fixation points
- Redock on the left (or right)
- Contralateral retromuscular dissection and transversus abdominis release
- Closure of posterior rectus sheath using slowly absorbable self-fixating suture
- Deployment of mesh
- Closure of hernia defect using slowly absorbable self-fixating suture

Single-Dock Technique

- Three right (or left) lateral abdominal wall trocars, with 4th assistant trocar placed, location at the discretion of the surgeon.
- Adhesiolysis and hernia reduction
- Removal of any prior intraperitoneal mesh
- Incision of ipsilateral posterior rectus sheath
- Retromuscular dissection from lateral to medial, ending at the linea alba
- Preperitoneal dissection along the midline, including reduction of the hernia sac
- Contralateral retromuscular dissection
- Contralateral transversus abdominis release (if indicated)
- Intracorporeal measurement of hernia defect
- Closure of hernia defect with slowly absorbable self-fixating suture
- Measurement of dissected space
- Placement of mesh (Vitamesh)
- Mesh fixation at minimum of 4 points

- Closure of posterior rectus sheath

Single-Dock Technique, Epigastric or Suprapubic Dock

- Three trocars along the upper or lower abdomen, with assistant trocar placed at surgeons discretion
- Adhesiolysis and hernia reduction
- Removal of any prior intraperitoneal mesh
- Transverse incision of bilateral posterior rectus sheath
- Bilateral retromuscular dissection, combined with midline preperitoneal dissection extending from at least 5cm below the defect to at least 5cm above
- Unilateral or bilateral transversus abdominis release (if indicated)
- Intracorporeal measurement of hernia defect
- Closure of hernia defect with slowly absorbable self-fixating suture
- Measurement of dissected space
- Placement of mesh (Vitamesh)
- Mesh fixation at a minimum of 4 points
- Closure of posterior rectus sheath

Perioperative Care

- Enhanced Recovery After Surgery (ERAS) protocol will be used for all patients as follows:
    - Preoperative electrolyte beverage 2-4 hours preop
    - Preoperative pain cocktail: (except in case of allergy or other specific contraindication)
        - Celebrex 400mg
        - Lyrica 75mg
        - Tylenol 1000mg
    - Avoidance of intraoperative narcotics
    - Ketamine bolus and infusion intraoperatively
    - Lidocaine infusion intraoperatively
    - Postoperative ketamine infusion continued on floor. Management of ketamine infusion by Anesthesia pain service
    - Postoperative intravenous acetaminophen and ketorolac (except in case of allergy or specific contraindication)
    - Oral narcotic (hydrocodone or oxycodone) given for breakthrough pain only
    - Oral intake beginning not later than morning of postoperative day 1

Management of Complications

- Surgical site infections will be managed by bedside or in-office opening and drainage of the surgical site, or percutaneous drainage of fluid collections as indicated, according with standard surgical principles.
- Operative intervention will be reserved for patients presenting with sepsis, or after failed non-operative therapy.
- Antibiotics at surgeon discretion.
- Surgical site occurrences (seroma or hematoma) will be treated only if patients have ongoing intractable pain related to the seroma, or there is concern for possible infection. Should intervention be required, simple aspiration, repeated as necessary, is the preferred approach, with percutaneous drain placement reserved for patients with suspected infection, or those requiring multiple reaspirations.

Follow-up:

Two week
6 week
6 month
1 year
2 years

Quality of Life

Will be assess via AHSQC Patient Reported Outcomes Quality of life questionnaire will be administered at preoperative visit and each planned postoperative visit, and will be administered by the Study Coordinator, Principal Investigator or Co-Investigator.

Sample Size & Statistical Analysis

Based on our current RRVHR outcomes and utilizing our entire OVHR database, which is maintained in a prospective fashion, we obtained a composite outcome using the combination of SSO (excluding seromas), SSI, hospital readmission, and hernia recurrence. For OVHR, the incidence of the composite outcome is 52.2% and for RRVHR 24.1%. Using a power of 80% and a significance of 5%, we estimate that 46 patients enrolled in each arm will demonstrate a difference in our primary endpoint. We plan to enroll at least 50 patients in each arm to allow for potential patient withdrawal or failure to maintain follow-up.

Differences in discrete primary and secondary outcomes (SSO, SSI, readmission, recurrence) between the OVHR and RRVHR groups will be analyzed using Chi-squared tests, or Fisher's Exact Test for small sample sizes ($N \leq 6$). Differences in continuous outcomes (length of stay, operative time, and costs) between the OVHR and RRVHR groups will be determined using students t-test and Mann-Whitney U tests. P-values <0.05 will be considered indicative of statistical significance. All analysis will be completed using R statistical software (R version 3.0.2).

Adverse Events: Defined as any unfavorable or any unintended sign, symptom or disease that is reported by the patient to have occurred, or a worsening of a preexisting condition. Adverse events will be recorded and detailed.

Potential Risks:
The following are possible complications specific to hernia repair, and may occur after either open or robotic repair:

- Seroma: A seroma is a collection of watery fluid below the skin that occurs in the space that is separated during surgery or in the space where your hernia was. This occurs in up to 50% of patients. This is almost always treated with observation. If treatment is needed, a small needle or tube may be placed to drain the fluid.
- Hematoma: A hematoma is a collection of bloody fluid below the skin that occurs in the space that is separated during surgery or in the space where your hernia was. This may occur in about 10-15% of patients. This is almost always treated with observation. If treatment is needed, a small needle or tube may be placed to drain the fluid.
- Skin dehiscence: Dehiscence is a separation of the skin at the site(s) of incision(s). This occurs in less than 5% of cases. Treatment may require a gauze or possibly a vacuum dressing to be placed in the wound until it heals. Healing time will depend on the size of the area of the incision that separates.
- Skin necrosis: Poor blood flow to a portion of the skin may cause it to die (necrosis). This occurs in less than 5% of cases. Treatment may be simple observation or may require removal of portions of the dead skin and fatty tissue. A gauze or vacuum dressing may be placed in the wound until it heals. Healing time will depend on the size of the area of skin necrosis.
- Surgical site infection: A surgical site infection is one that occurs in the skin or fatty tissue, in between the layers of the abdominal wall that are separated to repair the hernia, or inside the abdomen. This occurs in 5-20% of patients. Treatment may require antibiotics, opening of the incision, or placement of a needle or tube to drain the infection. If the incision is opened, a gauze or vacuum dressing may be placed in the wound until it heals. Healing time will depend on the size of the wound.
- Mesh infection: Infection may occur in the space where the mesh is located. This occurs in less than 5% of cases. Most often, this is treated exactly as other surgical site infection. However, if the infection does not go away, removal of the mesh may be needed. This is a rare.
- Bowel injury: Because we are working inside your abdomen, there is a risk of injury to your small or large intestine, which occurs in about 1% of cases. If this occurs and is seen at the time of surgery, it is repaired immediately. There is a small chance that a bowel injury could be missed, which may cause you to become seriously ill and likely require additional operation(s) to repair the bowel, prolonged hospital stay, or even result in death.

- Hernia recurrence: there is a 5-10% chance that your hernia will come back.

Any surgery has a risk of some complications, which may include:

- Venous thromboembolism (blood clot): Blood may clot within the vessels of the body, causing swelling of the leg(s). This occurs in about 2% of patients. If the blood clot breaks free from the vessels, they can travel to the vessels in the lungs, which can be fatal. Fatal blood clots are rare events. A blood thinner is needed for treatment. You will be given an injection of a blood thinner prior to the operation, as well as devices that will squeeze your calves, in order to prevent you from getting any blood clots.
- Respiratory complications, such as pneumonia or difficulty breathing. In rare cases, this may require you to be placed on a ventilator, a machine that assists in breathing, for a short period of time.
- Heart complications, such as heart attack, irregular heart rhythm, or heart failure.
- Ileus, which is a slowness of your intestine that may cause nausea or vomiting, may occur in 5-10% of cases. Treatment may require a tube placed through your nose to help empty your stomach.

Some of the questions in the quality of life questionnaire are of a personal nature and may be upsetting to some participants. Participants do not have to answer any questions that they do not want to answer.

This study may involve unknown risks to an unborn or nursing child. Women who are pregnant or nursing child may not participate in this study.

The study records are considered confidential, but absolute confidentiality cannot be guaranteed. This study may result in presentations and publications, but steps will be taken to make sure participants are not identified by name.

Potential Benefits:
It is not possible to know if there will be any potential benefit beyond what is expected for treatment utilizing the standard of care.

Potential Limitations:
Based on our current data, there is a shorter length of stay with robotic hernia repair compared to open, even though the remaining outcome measures (SSO, SSI, recurrence, SSOPI, SSIPI, readmission) are similar, which may bias patients against opting into randomization. This may not impact clinical outcomes, but could prolong the enrollment period. Patients may also be biased in favor of, or against, robotic repair based on patients' preconceived notion of either robotic or minimally invasive surgery.

Participant withdrawal: Participants may refuse to participate or choose to withdrawal from the study at any time without fear of being penalized or losing benefits. Participants may be

withdrawn from the study at any time if it is in the study Physician's judgment that withdrawal is in the participant's best interest, if the participant's medical condition changes or if the participant no longer follows the study instructions.

Informed Consent: The formal consent of a participant, using the GHS IRB approved informed consent form template, will be obtained by the study Physician before the participant undergoes any study procedures. The consent form will be signed and personally dated by the participant, a witness and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the participant's study records. A photocopy of the informed consent form will be scanned into the electronic system at the Vascular Health Alliance office. A photocopy of the signed informed consent form will be given to the participant for their records at the time of consent.

Safety and Reporting: Adverse Events, Serious Adverse Events and Unanticipated Adverse Device Effects will be reported to the GHS IRB according to OHRP policies 18.0 "Reporting of Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and 40.0 Appendices "Reportable Event Reporting Requirements - Appendix A."

Protocol Deviations: Protocol Deviations will be reported to the GHS IRB according to OHRP policy 20.0 "Non-compliance with Regulations, IRB Policies, Procedures or Decisions."

Privacy and Confidentiality: All data for this study will be kept confidential.

Costs: This study is not expected to yield any additional costs to participants. Participants will not be compensated to participate in this study.

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