RESEARCH PROTOCOL

TITLE OF PROTOCOL: A Randomized, Prospective, Double-Blind Clinical Trial Using Spy Elite System in Planning Tissue Advancement Flaps and Reducing Wound Complications after Complex Ventral Hernia Repairs

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PURPOSE OF PROJECT:

The purpose of this project is to assess the efficacy of the Spy Elite System in planning tissue advancement flaps and reducing wound complications after complex ventral hernia repairs. Complex ventral hernia repairs are associated with a high rate of wound complications. To a large degree these complications are caused by creating tissue advancement flaps to close the abdomen and compromising the blood supply to the skin and subcutaneous tissues. Current standard of care for assessment of blood perfusion to the flaps is a surgeon's clinical judgment. It is, however, often inaccurate. We would like to conduct a prospective randomized study to evaluate the efficacy of Spy Elite System in helping a surgeon to create tissue flaps with adequate blood supply. The Spy Elite System allows the surgeon to visualize tissue perfusion in real time. The pilot phase assessing the efficacy and safety of the Spy Elite system will be conducted first. For the second phase of the study, half the patients will be randomized to clinical assessment only group and half to the Spy Elite group. Patients will undergo follow-up at 1 to 2 weeks, 4 weeks and 12 weeks. Outcomes regarding wound complications will be recorded. Our hypothesis is that we will see decrease in wound complications in patients that had their tissue advancement flaps assessed with the Spy Elite System.

BACKGROUND AND SIGNIFICANCE:

More than 90,000 ventral hernia repairs are performed in the US annually [1]. Large ventral hernias often require a complex abdominal wall reconstruction including creating tissue advancement flaps. Complex abdominal wall reconstructions are associated with up to 20% rate of wound complications including skin flap necrosis and wound breakdowns [2]. Prevention of skin necrosis and ischemia would significantly reduce the morbidity associated with these procedures. Current standard of care for assessing the blood perfusion to the skin is a surgeon's clinical judgment. However, clinical assessment of flap perfusion is often inaccurate[3].

Spy Elite System is a device that enables surgeons to visualize and evaluate tissue perfusion in real time. It can help the surgeon to identify optimal flap design and reduce the risk of postoperative wound complications related to tissue ischemia. The Spy Elite System uses a fluorescence agent – "indocyanine green dye" – that is excited by near-infrared light. It is injected intravenously and has a half life of about 3 min. A high-resolution camera captures the image for display in real time. The blood vessels supplying the skin are visualized and a surgeon can design his flaps so that the blood supply is preserved. Spy Elite System has been used successfully for assessing the viability of mastectomy flaps in breast surgery. It has been shown to have an almost 100% sensitivity in predicting mastectomy flap necrosis, which is far better than a clinical assessment alone [4, 5]. The use of fluorescent imaging significantly increases the flap survival and reduces complications associated with mastectomies and breast reconstructions [3, 6]. Fluorescent angiography based on indocyanine green dye has also been used for other reconstructive procedures. It has been shown to be effective at evaluating vascular anastomosis and predicting the success of free tissue reconstruction [7].

Spy Elite System has never been used for assessment of abdominal cutaneous flaps in complex ventral hernia repairs. Based on the experience in breast and reconstructive surgery, it can be a useful adjunct in assessing the viability of skin and subcutaneous tissue in abdominal reconstructions. We propose a randomized clinical trial to look at the effectiveness of the Spy Elite System in planning the design of tissue advancement flaps for complex ventral hernia repairs and in prediction of postoperative wound complications.

The Spy Elite System uses indocyanine green intravenous contrast with its imaging. This dye has been used for over 50 years; in cardiac tests, hepatic function tests, and ophthalmologic testing. Side effects are very rare, but can be severe. A large series of injections reports side effect rates: 0.15% mild reactions, 0.2% moderate reactions, and 0.05% severe reactions. There were no deaths in this study with 1,226 consecutive patients and 1,923 indocyanine green tests[8]. FDA data reports potential anaphylaxis[9]. There have been studies suggesting increased rates of adverse reactions to indocyanine green dye in patients undergoing hemodialysis[10]. FDA data also shows that the exposure for the Spy system is 35 mW/cm^2 which is far below the maximum permissible exposure of 327 mW/cm^2 established by ANSI for exposure to the skin [11]

STUDY DESIGN, PROCEDURE AND FOLLOW-UP:

Patient Selection

Patients will qualify for this study if they meet the following criteria:

- Patients with ventral hernia that will require tissue advancement flaps at time of hernia repair
- Age ≥ 18 years
- Signed Informed consent

Patients will be excluded from the study if they meet the following criteria:

- ASA[1] score IV or above
- Age < 18 years
- Patients with Iodine allergy
- Patients with current wound or mesh infection
- Pregnant patients
- Patients with End Stage Renal Disease

Study Design

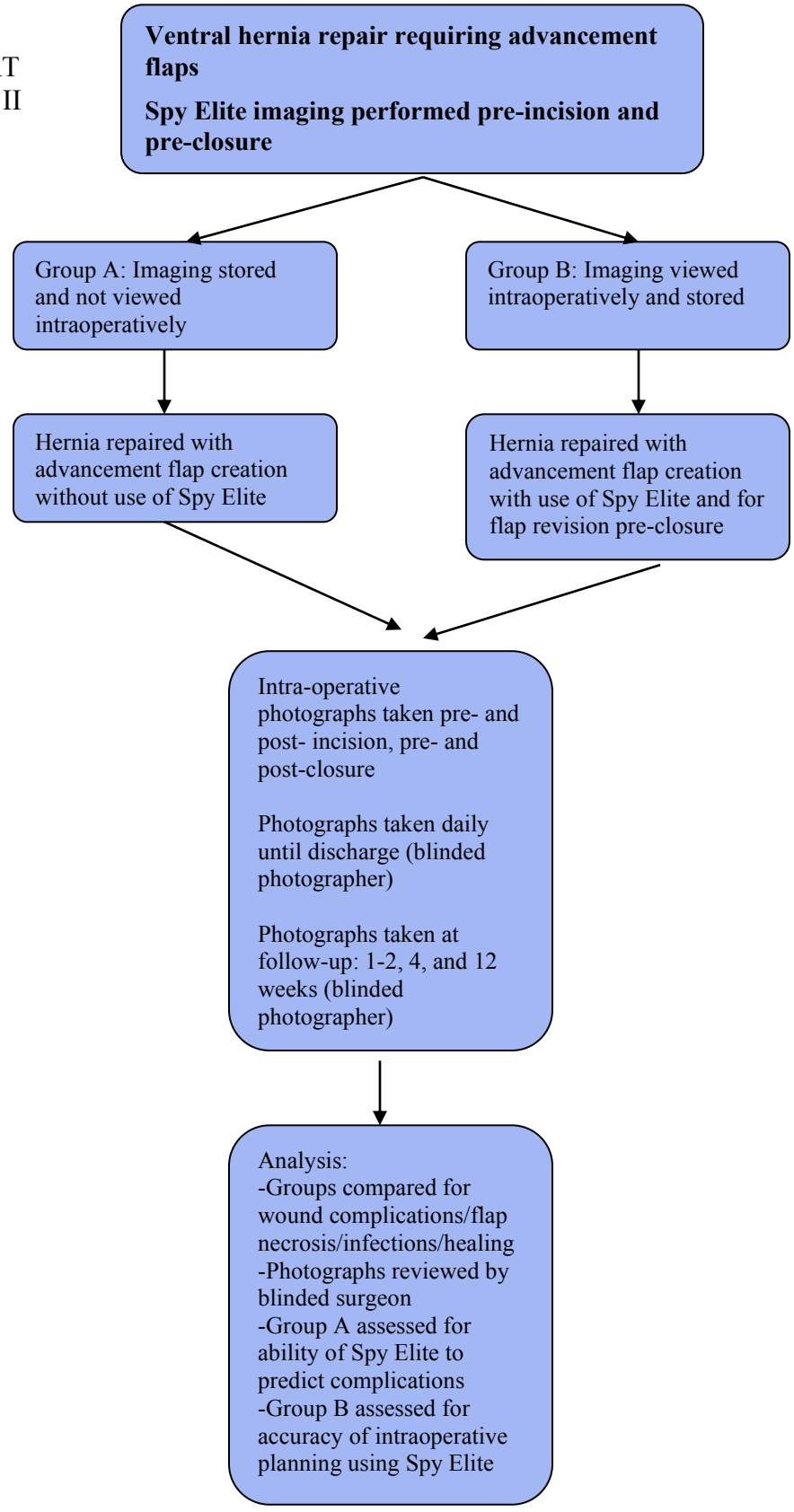
The study will be conducted in two phases. Phase I will assess the Spy Elite system's ability to predict advancement flap necrosis. It will consist of intraoperative abdominal wall imaging prior to incision, followed by ventral hernia repair with subcutaneous advancement flaps without viewing the imaging contained within the Spy Elite system. A digital photograph will be taken before and immediately after initial incision, as well as immediately prior to and after closure. A second set of Spy Elite images will be collected immediately prior to wound closure. The Spy Elite images will be stored and reviewed

[1] American Society of Anesthesiologists

after the follow-up period. The patient will have digital photographs of the surgical wound taken by the surgical team (general surgery and/or plastic surgery team) daily until discharge, and on follow-up visits at one week, two weeks, four weeks and twelve weeks. Given the lengthy travel distance for some patients, the research team will offer patients the option to take and send the research staff a photograph at each of these follow-up time intervals. If participants did not attend a follow up visit on site, the research team will contact patients after the 12 week follow up time point to offer the option to send in pictures to the research staff. If a patient remains hospitalized beyond seven days, the daily wound photographs at corresponding time points will be used in the place of outpatient follow-up photographs. After twenty patients have completed phase I, the surgical team will be unblinded to Spy Elite imaging. The Spy Elite imaging and all digital photographs of all patients will be reviewed. The ability of the Spy Elite system to predict skin flap necrosis will be assessed based on preoperative blood supply assessment by the Spy Elite system, photographs of incision used, and follow-up photographs of the wound.

Phase II will consist of a randomized prospective trial to assess whether the Spy Elite system can be used to reduce advancement flap necrosis. All patients will undergo intraoperative abdominal wall imaging prior to incision, as well as imaging prior to wound closure. Patients will be randomized to whether or not their Spy Elite imaging is reviewed in the operating room. One half of the patients (group A) will be treated identically to the patients in phase 1 while in the operating room. The other half (group B) will have incision and advancement flap performed based on assessment of blood supply using the Spy Elite system, as well as potential flap revision if portions of the flap appear under-perfused in the pre-closure imaging. Both groups will have immediate pre- and post-incision digital photograph taken, as well as immediate pre- and post- closure digital photographs. Patients will be blinded to whether or not their intraoperative Spy Elite imaging was used for operative planning. All patients will have digital photographs of the surgical wound taken by a blinded member of the surgical team (surgical fellow, resident, physician extender, or nurse) in the surgical ward daily until discharge, and on follow-up visits at one to two weeks, four weeks, and 12 weeks post-operatively. If the patient cannot visit the site, research staff will later offer patients the option to take and send the research staff a photograph. Digital photographs will be reviewed by a blinded surgeon, who will assess the wound for complications (breakdown, necrosis, erythema, infection, or dehiscence with location specified) and assessment of healing. Research staff will complete follow up with patients who demonstrate no wound complications in order to ensure that late developing complications are not missed. Upon study completion, groups will be compared for wound complications, presence of flap necrosis, quantification of flap necrosis, and healing speed. Patients randomized to the group A will also be examined identically to phase I patients to further assess the ability of the Spy Elite system to predict wound complications. Imaging and photographs of group B patients will be used to determine if appropriate operative planning was performed based on intra-operative imaging. Based on results from phase I, a cost-benefit power analysis was performed. It was determined that 102 patients will be required for enrollment of phase II of this trial. During phase II, we will be obtaining external funding and compensating enrolled patients $50.00 for their participation in study.

FLOWCHART
FOR PHASE II



Endpoints

Primary endpoint of the study is a composite endpoint of surgical wound complications and includes:

- skin necrosis (will be quantified based on the area involved)
- wound dehiscence
- wound abscess
- cellulitis
- seroma
- hematoma
- bedside or operative interventions
- use of antibiotics

Secondary endpoints are:

- duration of surgery
- length of hospital stay
- cost effectiveness
- incidence of adverse reactions to indocyanine green dye

Preoperative Assessment

All patients eligible to take part in this trial will be informed. The decision to use the technique of tissue advancement flaps for wound closure will be based entirely on clinical grounds. Once it is determined that patient will need a complex wound closure, he or she will be offered the patient information letter ("Patient Information Form") and asked to sign the informed consent. The consent will contain information about the possible side effects associated with the use of indocyanine green dye as well as permission to collect data, take photographs of the patients' surgical sites, distribute surveys and contact them after surgery for educational and research purposes. Patients willing to enroll will be assigned to either the clinical assessment group or Spy Elite group based on the randomization. To date, there is no data to support the superiority of either method of flap assessment in abdominal wall reconstructions.

Randomization

Randomization will be performed by a certified statistician using a computerized algorithm. Stratified randomization will be used based on the demographics and comorbidities in order to maximize the likelihood of balanced groups. Patients will remain unaware of their group assignment or which method of flap assessment was used in their groups.

Method of Repair and Intra-Operative Procedure

On the day of surgery, each patient will be randomized into one of two groups. A group assignment letter in a sealed opaque envelope will be placed into patient's chart. The chart will be marked with a sticker identifying the patient as part of proposed clinical study. Prior to taking the patient back to the operating room, the circulating nurse will

check that the patient is appropriately consented and understands that he/she is enrolled in the study. Furthermore, the circulating nurse is responsible for ensuring that the sealed envelope is in the chart and has not been opened. Following patient transfer to the operating room and induction of anesthesia, the circulating nurse will perform a "time-out", where he/she reads the consent form and notifies the operating room that the patient is part of the proposed study. As part of the time-out, the circulating nurse will open the sealed envelope and announce the group assignment to the surgical team prior to the start of the procedure. This will give sufficient time for the staff to obtain all necessary materials.

Indocyanine green dye will be injected intravenously prior to incision and the images of the abdominal skin will be recorded with Spy Elite system. If a patient is assigned to group A, the image will be stored away and not looked at. If a patient is assigned to group B, the image will be reviewed and the incision will be planned according to the vascular map. If panniculectomy is planned, this will be the first part of the procedure. The advancement flaps will be created.

The hernia will be repaired primarily or with mesh and that decision will be made by a surgical team based on clinical grounds only. Mesh can be placed in any position, and the placement will be determined by a surgeon according to his best judgement. Unilateral or bilateral component separation may be performed if deemed necessary by a surgical team. Skin will be closed with staples or monofilament suture according to surgeon preference. One or two drains will be placed on the mesh (if it is used), and two drains will be placed in the subcutaneous tissues. Patients will receive a second injection of indocyanine green and the images of the advancement flaps will be recorded with Spy Elite camera. If a patient is assigned to group A, the pictures will be stored away and not looked at and, the flaps will only be assessed clinically. If a patient is assigned to group B, the pictures will be reviewed intra-operatively and the ischemic parts of the flaps will be trimmed according to the vascular map and clinical appearance. Prior to closure, the subcutaneous space will be irrigated with pulse lavage irrigation and sprayed with talc.

Post-Operative In-Hospital Care

All patients will be admitted to the hospital for postoperative monitoring. Depending on the preoperative diagnosis and concomitant procedures, patients will typically stay in the hospital for a period of 4-7 days. Intravenous antibiotics will be administered to patients with infected wounds and at the discretion of the attending surgeon following CDC guidelines. Early clinical outcomes will be documented as related to return of GI motility, respiratory status, renal function, pain control, and ambulatory status. Criteria for discharge will include absence of fever (temperature >100.5oF), adequate oral intake to maintain hydration and nutrition, and adequate pain control with oral analgesics as determined by the attending surgeon.

Safety Monitoring

Safety issues that may terminate the study are reaction to indocyanine dye used with the Spy Elite system (0.15% risk of mild reactions, 0.2% moderate, 0.05% severe[8]),

significant differences in 30 day mortality and unplanned reoperative interventions, as well as wound breakdown, infection, necrosis, or wound dehiscence. Given the inherently high rates of infection of grade III and IV wounds, any observed differences in complication rates will be rigorously investigated prior to any sanctions on study continuation. Any unexpected mortality will be reported directly to the IRB for their review. Any complications that are directly attributed to the Spy Elite system or indocyanine green injection will also be reported to the IRB. Ronald F. Sing, D.O. will perform the role of safety monitor for this study and will be informed of any untoward complication including a surgical site infection, seroma or hematoma formation, wound dehiscence, postoperative evisceration, or mortality within 48 hours. In concordance with operating surgeons, any uncomely events or data as listed above will be reported to the IRB.

Outpatient Follow-Up

Patients will undergo post-operative follow-up at 1 to 2 weeks, 4 weeks and 12 weeks. At each visit patients will be examined by a board certified surgeon who performed the operation or his associate and patients will be treated according to current standards of clinical practice. During each follow-up visit a photograph of the patient's incision will be taken by a registered nurse who is blinded to the patient's group assignment. A ruler will be placed next to the incision before the photo is taken for the size estimates. The photos will be reviewed by a board certified surgeon who is blinded to the patient's group assignment and who will then fill out form A. The wound complications including skin necrosis, wound dehiscence and cellulitis will be recorded in the form. In the event that a patient fails or is unable to complete the post-operative12-week follow-up visit in person, a member of the research study (MD) will later contact the patient via telephone. The patient will be asked to provide a digital or physical photograph of the incision via email or mail to the research team for inclusion in this study. The telephone interview script (form B) is appended to this protocol.

STATISTICAL PROCEDURE:

For the pilot phase, we will enroll 20 patients. The data from this phase of the study will be used to determine the sample size necessary for the second phase of the study via a power analysis. Based on results from phase I, it has been determined that N=102 patients will be required for enrollment of phase II of this trial. We anticipate minimal attrition due to the short follow-up period and based on our experience with Phase I. However, attrition rates will be assessed once enrollment has reached N=51 (midpoint) and we will increase our target enrollment if necessary.

Demographics, comorbidities, preoperative conditions and the nature of contamination will be recorded as well as post-operative hospital course and follow-up findings, including drain outputs, the use of antibiotics and drainage procedures, and postoperative quality of life surveys. The latter along with hernia recurrences and specific wound complications will be used as primary outcome variables.

Statistical analysis will be performed using SAS® System version 9.2 (SAS, Cary, NC, USA). Continuous variables will be compared using Student t-test and Wilcoxon-Mann-Whitney test. Frequencies of complications will be analyzed using Chi-square and Fisher's exact test. Differences in demographics and preoperative data will be controlled using linear and logistic statistical modeling techniques. Once confounders are determined, the effect of the Spy Elite System on patient outcomes and quality of life will be analyzed using multivariate regression. The significance level will be set at $p<0.05$ for all analyses.

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FORM A:

Examiner: _____

Circle Appropriate Answers

Is there skin necrosis?

Yes / No

If yes, what area is necrotic (approximately)? _____(cm2)

Is there cellulitis around the incision?

Yes / No

Does the wound appear infected?

Yes / No

Is there a wound breakdown?

Yes / No

If yes, what is the length of the breakdown?_____(cm)

Are there signs of normal healing?

Yes / No

Please describe any abnormal healing not addressed above_____

Please indicate any other significant findings:_____

Form B:

Telephone Follow-Up Interview Script

"Hello, my name is Dr. (Research assistant or fellow, i.e. Samuel Ross) from Dr. (Heniford, Augenstein, Kercher, Getz)'s office at CMC Surgery."

"Our records show that you are a participant in a study on utilizing a new piece of surgery imaging for hernia patients, entitled *A Randomized, Prospective, Double Blind Clinical Trial Using Spy Elite System in Planning Tissue Advancement Flaps and Reducing Wound Complications after Complex Ventral Hernia Repair* and underwent an abdominal hernia repair by Dr. (Heniford, Augenstein, Kercher, Getz) on (date). Is this correct?"

If no . . . "I apologize for the interruption, thank you for your time and have a great day."

If yes . . .

"We are calling Dr. (Heniford, Augenstein, Kercher, Getz)'s patients to ask about this previous surgery. Would you mind answering a few questions for me?

If no . . . "I apologize for the interruption, thank you for your time and have a great day."

If yes . . .

"Thank you."

"Have you been treated by any other physician other than Dr. (Heniford, Augenstein, Kercher, Getz) for complications associated with your surgery?"

If no . . . Proceed to question on pain after surgery (below).

If yes . . . "Can you tell me more about the treatment you received? Were you prescribed antibiotics? Was your wound opened or drained?"

"Have you been admitted to any other hospital, other than CMC, for complications associated with the surgery?"

If no . . . Proceed to pain question (below).

If yes . . . "Can you tell me more about the treatment you received? Were you given antibiotics? Was your wound opened or drained? Did you have to have an operation?"

→ "Are you still having pain associated with the hernia repair?"

If no . . . "We appreciate your participation in this study. " Proceed to photograph question.

If yes . . . "Can you describe the pain, and what you do to treat it?"

"Would you be willing to provide us with a photograph of your previous incision so that our researchers can study how well your wound has healed?"

If yes… "Thank you,; please send your picture to CLASP.research@CarolinasHealthCare.org or you may mail it to us at 1025 Morehead Medical Drive, Suite 300, Charlotte, NC 28204. If you like, we can email or mail you a reminder to send us this picture. Thank you for your time and for participating in this study."

If no… "Thank you for your time and for participating in this study. "

"Lastly, do you have any additional comments regarding your hernia operation?"

"Thank you so much for your time, have a great day."