# PROTOCOL

## Background

**1. Provide the scientific background, rationale and relevance of this project.**

There are many surgical wound closure methods commonly used in orthopaedic surgical practice today. These usually involve a combination of braided and monofilament sutures in the subcutaneous fascia and fat as well as the subcuticular layers of the skin. The methods chosen by surgeons vary widely even amongst partners at the same institution for many reasons, including training background and conflicting reports in the literature about optimal techniques. In some cases, these closure techniques can be time consuming and associated with increased rates of poor cosmetic outcomes or complications.[1–4] Wound management has also become an increasingly important factor in patient satisfaction.[5] There have been new wound closure products to reach the market (Zipline - Campbell, CA and Clozex - Wellesley, MA), claiming to increase the speed of closure, improve patient satisfaction and decrease the rate of complications.[4,6–9] These products are FDA approved and both utilize an adhesive backed film to adhere to the skin along with a proprietary mechanism to promote skin apposition and reduce tension during the healing process. They have been shown to be safe and effective treatment options and have been adopted in many practices.[10]

Our study aims to compare a traditional wound closure using both braided and monofilament sutures to the newer wound closure systems. By determining which method provides superior results, we will improve patient outcomes and satisfaction. The study also aims to assess health care value by exploring the costs associated with each closure technique. In addition to material expenses associated with the traditional sutures, we seek to explore if there is a significant difference in the time required to perform each wound closure method. Every minute of anesthesia and operating room utilization is associated with costs borne by the patient and the health care system. By finding which closure method is the fastest and associated with the best outcome we can improve healthcare value.

Our primary objective outcome measure will be an assessment of surgical scar characteristics using the Stony Brook Scar Evaluation Scale (SBSES) which has been validated in the assessment of surgical scars in the first year after surgery.[11,12] Secondary outcome measures will include adverse events related to the surgical wound, surgical time for closure, a patient satisfaction score and physician satisfaction score.

## Objectives/Hypothesis

The objective of this study is to compare commonly performed wound closure methods in patients undergoing orthopaedic surgical procedures. The primary outcome measure is SBSES score. Secondary outcome measures include wound adverse events, surgical time, patient satisfaction scores, surgeon satisfaction scores and to determine any difference in the costs associated with each of the wound closure techniques. Our null hypothesis is that there will be no significant difference in terms of wound complication rates, patient satisfaction and surgeon satisfaction scores.

## Study Design: Biomedical

**1. Will controls be used?** YES

►**IF YES, explain the kind of controls to be used.**
The control will include an all-suture based wound closure consisting of braided Vicryl suture in deep fascia/fatty layers followed by monofilament 3-0 Monocryl subcutaneous suture and running 3-0 prolene subcuticular suture.

**2. What is the study design?**
Randomized control study

**3. Does the study involve a placebo?**
NO

## Human Participants

**Ages:** 18+
**Sex:** Male and Female
**Race:** All

**Subjects**

**1. Provide target # of subjects (at all sites) needed to complete protocol.**
Surgical subjects: 30
Clinicians: 10

**2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.**
Surgical subjects: About 36%
Clinicians: 0

**3. How many subjects will be enrolled at all sites?**
Surgical subjects: 83
Clinicians: 10

**4. How many subjects will sign a consent form under this UVa protocol?**
Surgical subjects: 83
Clinicians: 10

## Inclusion/Exclusion Criteria

**1. List the criteria for inclusion**
Surgical Subjects:

- Age 18+
- Patient scheduled to undergo elective orthopaedic surgical procedure with a minimum anticipated incision length of 3 cm.
- Willingness and ability to comply with scheduled visits and study procedures.

Clinicians:

- Attending surgeons, physician assistants and trainees (fellows and residents) in the orthopaedic surgery department
- Willingness to comply with randomization and study protocols

**2. List the criteria for exclusion**

Surgical subjects:

- Revision Surgery
- Compromised wound healing (autoimmune disorder, chronic steroids )
- Pregnant women, fetuses, neonates, children, prisoners, cognitively impaired, educational or economically disadvantage, non-English speaking subjects.
- Currently taking Immune modulating (DMARD) medications will exclude patient from participation in study
- Currently taking Chronic Steroids

Clinicians:

- None

3. **List any restrictions on use of other drugs or treatments**.

## Statistical Considerations

**1. Is stratification/randomization involved?** YES

**►IF YES, describe the stratification/ randomization scheme.**

Simple randomization will be used. A random number generator will be used to devise a list to assign study numbers to treatment groups, ensuring that there will be equal numbers assigned to each group. No other variables will be used for stratification. For each study number, the treatment assignment will be placed into an envelope by the clinical trials coordinator and sealed.

There will be no blinding of subjects or personnel involved in the study once the envelope with group assignment has been opened.

The statistician doing the randomization and the clinical trial coordinator will be the only ones with access to the master treatment assignment list.

**►IF YES, who will generate the randomization scheme?**

_____ Sponsor
__X__ UVa Statistician: Wendy Novicoff
_____ UVa Investigational Drug Service (IDS)
_____ Other*:*

**2. What are the statistical considerations for the protocol?**

Primary outcome variable: SBSES scores will be assessed at scheduled post operative visits. The minimal clinically important difference will be defined as 1 point. The null hypothesis is that

there will be no difference between the SBSES scores between treatment groups (one-way ANOVA).
Secondary outcome variables: patient satisfaction with appearance of scar (on scale of 1-10), physician satisfaction with the technique/device (on a scale of 1-10), and presence or absence of adverse events (including infection and reoperation). For the scaled scores, descriptive statistics will be calculated, and means between groups will be compared (one-way ANOVA). A count of the adverse events per group will be tallied.

**3. Provide a justification for the sample size used in this protocol.**
Based on research from Agarwala and Vijayvargiya (2019), average SBSES is 4.4 (SD = 0.73) for a post-operative orthopaedic surgical incision. If we are using a one-way ANOVA, alpha = 0.05, and power = 0.80, we would have the following sample sizes required for each group based on various differences between groups.

| Difference in means between groups | Standard deviation | Sample size required (for each group) |
|---|---|---|
| 2 | 0.73 | 4 |
| 1.5 | 0.73 | 6 |
| 1 | 0.73 | 10 |
| 0.5 | 0.73 | 43 |

We will be enrolling up to 20 patients per group to ensure that we will have 10 patients for analysis in each group.

**4. What is your plan for primary variable analysis?**
Primary outcome variable: SBSES score. A one-way ANOVA will be employed to compare mean scar assessment scores between groups.

**5. What is your plan for secondary variable analysis?**
Secondary outcome variables: patient satisfaction with appearance of scar (on scale of 1-10), physician satisfaction with the technique/device (on a scale of 1-10), and presence or absence of adverse events (including infection and reoperation). For the scaled scores, descriptive statistics will be calculated, and means between groups will be compared (one-way ANOVA). A count of the adverse events per group will be tallied.

Cost analysis between approaches will be assessed using the following metrics: the cost of operating room time per minute will be multiplied by the time for closure and added to the cost of materials to determine a total cost for each approach. The average costs for each approach will be compared using a one-way ANOVA to determine if there are significant differences in costs.

**6. Have you been working with a statistician in designing this protocol?**

YES

**IF YES, what is their name?**
Wendy Novicoff

**7. Will data from multiple sites be combined during analysis?** NO

## Study Procedures-Biomedical Research

**1. What will be done in this protocol?**

Patients who meet above inclusion criteria and provide informed consent will be enrolled in the study. All members of the research team that will be assisting with the surgical closure (including attending surgeons, fellows, residents and/or physician assistants) will receive full training in the application of both the Clozex and Zipline devices to insure uniform experience among participants. The clinicians performing the closure are also investigators in this research and may opt out of participating in this study. There are no pre-operative study procedures for the patients, aside from a review of inclusion and exclusion criteria and enrollment.

On the day of surgery, the enrolled subject will be randomized into one of three study groups. The randomization will occur during surgery, prior to wound closure. The circulating nurse will open an envelope, which will determine the randomization group for the subject. This will allow operating room staff the time to assemble the appropriate materials for closure depending on participant's group assignment without any delay to standard of care. The subjects' randomization into a treatment group is not expected to significantly increase the time of the operation or duration of anesthesia. The wound closure will proceed as follows:

1. Any deep fascial layers will be closed with braided Vicryl suture as indicated and according to standard of care.
2. The subcutaneous fat will be closed using 3-0 Monocryl in inverted, interrupted fashion according to standard of care.
3. The circulator will then start a timer that will run until the wound is completely closed.
    A. If randomized to the **Control group**: Closure will proceed with a running 3-0 Prolene subcuticular suture with escape stitches.
    B. If randomized to the **Clozex treatment group**: Closure will proceed with application of the adhesive device according to manufacturer's recommendations
    C. If randomized to the **Zipline treatment group**: Closure will proceed with application of the adhesive device according to manufacturer's recommendations
4. If at any time, the surgical provider (attending surgeon, fellow, resident, PA) determines that the device in the test group has failed (i.e. adhesive failure, device breakage), s/he may elect to proceed with suture closure and study cross over shall be recorded.
5. At the conclusion of the wound closure, the timer will be stopped and the operative time will be recorded.

Dressings will then be applied in standard fashion including 4 x 4 gauze, webril wrap and ACE bandage and splinting as indicated. The team member who performed the wound closure (attending surgeon, fellow, resident or PA) will fill out the survey on satisfaction with the closure (scale 1 – 10) and note any complications or confounding factors (challenging incision pattern or application problems). The subject will be discharged with standard wound care instructions to keep the surgical dressing in place for 3 days and then to replace it with clean sterile dressings. The subjects will be cautioned not to submerge their wound underwater for at least 2 weeks following surgery, as per standard protocol.

Initial follow up will occur at a standard time interval within 14 – 17 days after surgery, at which point Prolene sutures will be cut and removed and Clozex/Zipline devices will be removed. An assessment of the wound will take place by the same attending surgeon who performed the procedure using the Stony Brook Scar Evaluation Scale (SBSES) using the below rubric (scale 0 – 5).

| Category | | Points |
|---|---|---|
| Width | > 2 mm | 0 |
| | ≤ 2 mm | 1 |
| Height | Elevated/ depressed in relation to surrounding skin | 0 |
| | Flat | 1 |
| Color | Darker than surrounding skin | 0 |
| | Same color or lighter than surrounding skin | 1 |
| Hatch marks/Suture marks | Present | 0 |
| | Absent | 1 |
| Overall appearance | Poor | 0 |
| | Good | 1 |

A brief survey will then be completed by the study participant to rate their satisfaction with their surgical scar on a 1 – 10 scale. The physician or physician assistant seeing the subject in follow up will document the presence or absence of adverse events (including infection and reoperation).

The SBSES assessment, adverse event monitoring and patient satisfaction will be recorded at a second standard of care follow up visit between 10 – 14 weeks after surgery. The subject will be released from the study after the final standard of care follow up visit occurs, and will no longer need surveillance or monitoring.

Cost analysis between the groups will be assessed using the above statistical approach. To carry out this analysis, we will obtain: 1. Cost for all materials needed for wound closure, 2. Amount of time (in minutes and seconds) needed to close the wound (start time = all supplies are gathered to close the wound, and stop time = wound is declared fully closed), and 3. Operating room costs (including overhead) per minute.

**2. If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.**

The patients that are involved in the study treatment groups will have the same post operative management as the control group. At the 2 week visit, the devices (Clozex or Zipline) will be removed and all groups will have the same wound care instructions.

## Subject Compliance with Study Procedures

1. **Explain how the study team will monitor the subject for compliance with the study procedures.**

Participants in the study will have the same post-operative instructions as all patients undergoing elective orthopaedic surgical intervention with the exception of a brief survey completed at the post-operative visits. Their participation in the study does not require any additional active steps or procedures to be completed. Thus, compliance in the study will only require observing basic post-operative wound care instructions and returning for routine follow ups.

2. **Describe criteria for when a subject is considered to be non-compliant with study procedures.**

A study subject would be considered non-compliant if they were to remove the sutures or devices on their own, fail to return for at least 2 post-operative wound check visits or fail to complete the required survey.

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