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White Paper

Wound Closure

MEDICAL DEVICE

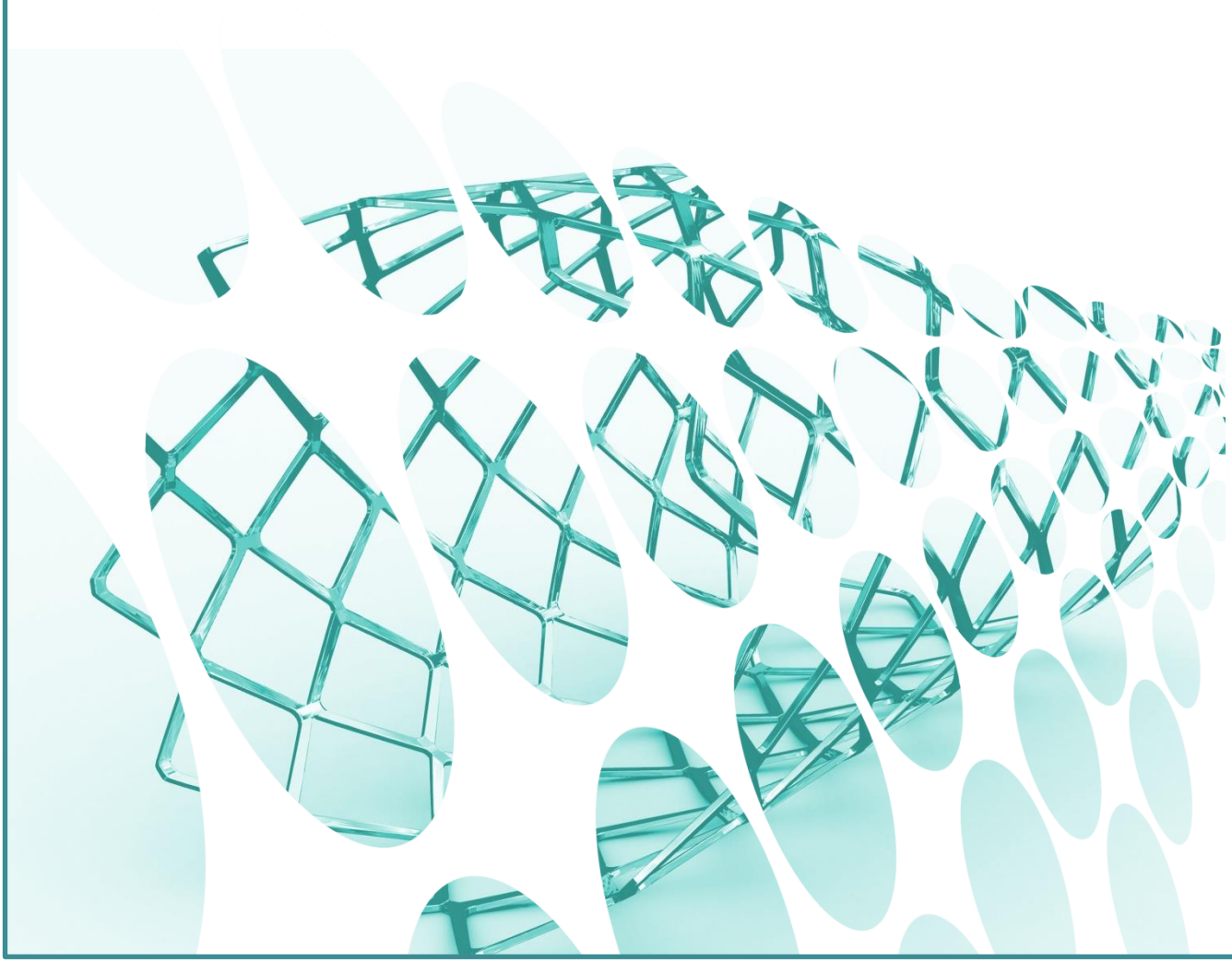


Table of Contents

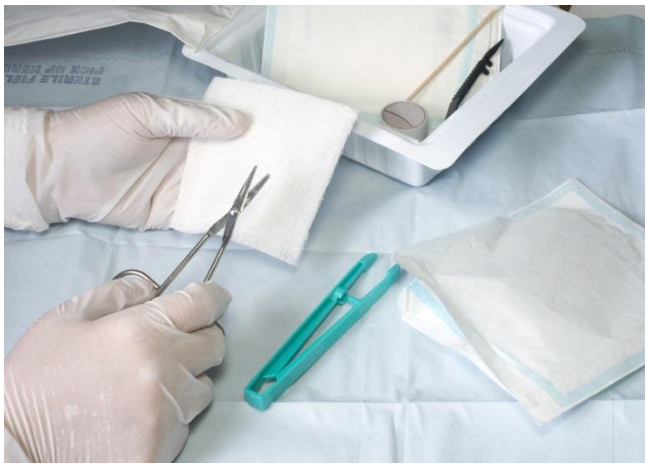
1. Introduction

Wound closure trials are becoming increasingly common due to scientific advances in creating adhesive tapes and strips and tissue adhesives to substitute for sutures and staples, ever striving for the best possible aesthetic outcome.

The ideal wound closure device is strong, flexible, easily applied, and results in an excellent cosmetic outcome for the patient. It may be biodegradable or not, depending on the situation, and it must be durable for the anatomical location, resisting wear and washing until the wound is adequately healed to maintain closure without the device remaining in situ.

This paper reviews several important issues to be taken into consideration when designing and performing studies of wound closure products. For simplicity, this paper will concentrate on the study of devices to close surface wounds such as incised wounds due to surgery or trauma.

2. Primary Endpoint: Wound Closure



The most important role of a wound closure device is …… to close the wound. The primary effectiveness endpoint is therefore usually an assessment of the extent of continuous apposition of the wound (skin) edges at regular time points during the study. Surface wound healing is normally complete in 10-14 days, so it is normal to plan post-procedure visits at around Day 2-4 (to ensure that there is no significant wound dehiscence that requires further intervention) and Day 10-14 (to assess final wound closure).

It is important to control for those factors that will directly influence wound closure such as the ease with which the skin edges can be brought into apposition at the time of wound closure. If the wound is “tight”, the wound closure device will fail more often to bring the edges into apposition. The protocol must make clear if deep dermal or other sutures are allowed to reduce the tension on the superficial wound closure devices.

Other factors that influence wound closure are systemic or local infection, the presence of concurrent medical conditions such as poorly controlled diabetes, and the anatomical location and perfusion of the wound.

The best way to control these factors that influence wound closure and healing is to ensure that there is a control group, that patients/wounds are randomized to one device or the other, and that wounds with high risk of poor healing are excluded.

3. Secondary Endpoint: Cosmetic Outcome

There are several different scales and scores that are used to determine cosmetic outcome. The one that is most frequently used (and mentioned in FDA guidance on assessing cosmetic outcomes) is the Modified Hollander Cosmesis Score. It is a validated score, but originally designed for short-term, "in person" outcome assessment. There are instances of this score being used to assess outcomes six and twelve months after the initial procedure, and being used to assess wounds from photographs. As you can see from the photographs above, the assessment of wounds from photographs, even those taken under standard conditions, is not an easy task. Cosmetic outcome is usually measured post-procedure at Week 6 and Week 13, and sometimes at Week 26 and Week 52. The same person should assess the wound throughout the study.

Modified Hollander Cosmesis Scale

Evaluation Characteristics	Yes (Poor)	No (Good)
a. Step-off Borders	1	0
b. Contour Irregularities	1	0
c. Wound Margin Separation	1	0
d. Edge Inversion	1	0
e. Excessive Inflammation	1	0
f. Overall Appearance	1	0

It is also common to have a global assessment score completed by the patient and the clinician to describe the overall cosmetic appearance of the wound at the end of the study.

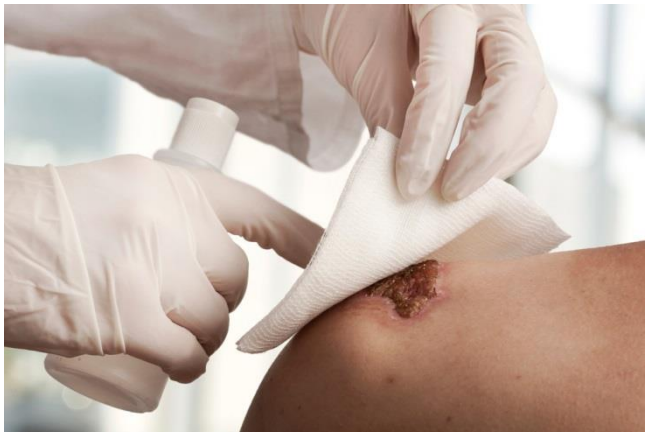
4. Safety Endpoints

One of the main tools to assess safety is a score to assess the wound periodically during the trial. Many of these are not validated but are based on scores used to assess skin reactions in toxicology studies (Draize Scores). For example, the erythema, edema, tenderness to palpation, and temperature of the wound may be measured by the clinician on a five-point

scale at all study visits. The patient may rate the pain of the wound using a 100mm visual analogue scale also at all study visits.

Adverse events should be recorded as spontaneously volunteered throughout the study. Verbatim adverse event terms are sometimes unhelpful when trying to decide if the adverse event applies to the target wound or not. We recommend adding a check box to the AE form to show which adverse events apply to the target wound.

5. Control Group



In order to control for the many factors that affect wound closure and healing, it is usual to include a control group in the study. This is often the "gold standard" wound closure method or the method that is most commonly used. In many cases this will be non-resorbable sutures. The function of the control group is to standardize as much as possible extraneous factors such as concomitant disease and medication between the treatment groups.

One of the best controls is to have two identical wounds in the same patient. One wound is treated with the investigational device and the other with the control. Bilateral breast surgery is often used as a model for this type of intra-patient control.

Both treatment groups receive otherwise standard care, particularly in terms of post-procedure instructions about caring for the wound, such as how long to keep the wound covered or dry, and when any dressings or the devices themselves should be removed. This influences site selection: all sites must be prepared to use the control device and must be compliant with the post-procedural instructions in the protocol that they and the patient must follow.

6. Patient Recruitment and Retention

In order to recruit well, sites must be appropriate to the wounds to be included in the study. In general, smaller, incised wounds and lacerations (if these latter wounds are not excluded) are treated in the ER, and longer incised wounds are recruited from a surgical unit.

Those patients with smaller wounds may not feel the need to come back for follow up visits, particularly when the cosmetic outcome is good. In addition, most ERs are not set up to follow patients after the initial intervention. It is important in these situations to select sites that have an aftercare facility so that patients can continue to be followed for study visits. This issue is less troublesome if the site is a surgical unit, as facilities for follow up of

patients usually readily exist.

These arrangements for follow up may impede monitoring, as records needed to source data verification may exist in different locations. Patient records in surgical units may be difficult to navigate as much information is recorded about the surgical procedure itself, including copious anesthetic records.

7. Study Design Points to Consider

The study design needs to cater for patients having more than one wounds. The options are to choose one wound as the target wound and randomize by patient, ignoring the other wounds for the purposes of the study. The second option is to choose one target wound, but treat all the wounds with the same treatment to which the target wound is randomized. Thirdly, each wound could be randomized separately within the study. This is rather cumbersome, especially for keeping track of which wound was treated with which device. In all these cases, the disadvantage of including patients with multiple wounds is that the condition of one wound may affect the other wounds.

8. About CROMSOURCE

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