Incisional negative pressure wound therapy for preoperatively irradiated pelvis and lower extremity soft tissue sarcoma wounds. A prospective, randomized pilot trial.

NCT02638298

Date Last Modified: April 21st, 2023

Principal investigator

Lee R. Leddy, M.D., MSCR
Associate Professor Orthopaedic Surgery
Orthopaedic Oncology
Director of Orthopaedic Research
Associate Program Director
Medical University of South Carolina

96 Jonathan Lucas St MSC 622
Charleston, SC 29425
Phone: (843) 792 5607
Fax: (843) 792 3843

Table of Contents

Medical University of South Carolina
Protocol
PI Name: Lee Leddy, MD, MSCR

Study Title: **Incisional negative pressure wound therapy for preoperatively irradiated pelvis and lower extremity soft tissue sarcoma wounds. A prospective, randomized pilot trial.**

A. HYPOTHESIS/SPECIFIC AIMS

The hypothesis of the proposed study is that use of a negative pressure wound therapy (NPWT) dressing on preoperatively radiated pelvic and lower extremity soft tissue sarcoma surgical wounds will significantly reduce the incidence and cost of wound complications.

This hypothesis will be tested through accomplishing the following specific aims:

1) Specific Aim 1- To estimate the wound complication rate of post-operative negative pressure dressings and traditional dry dressings, and risk of secondary interventions after resection of soft tissue sarcoma in lower extremities and the pelvis that have received pre-operative radiation. Wound complications are defined as a superficial infection, deep infection, need for prolonged (> 3 weeks) wound packing, or return to the operating room within six months for a secondary procedure. A secondary analysis of frequency and likelihood of antibiotic usage, pain scores, and functional scores will be analyzed in each group.

2) Specific Aim 2- To estimate the total cost of care and resource utilization in patients treated with negative pressure wound therapy and traditional dry dressings.

B. BACKGROUND AND SIGNIFICANCE

Patients with sarcomas who receive preoperative radiation have over twice the incidence of wound complications (35%) when compared to those who receive post-operative radiation (17%)[1]. Postoperative surgical site wound healing problems pose a significant challenge to the orthopaedic oncologist, especially in wounds that have been previously irradiated with neoadjuvant external beam radiation therapy (EBRT). Wound healing after major oncologic resection in the lower extremity is often compromised. In sarcoma patients this is especially true where patients tend to be older than age 50 and most receive preoperative radiation prior to resection to assist in local control. There are many studies demonstrating the relatively high risk of wound complications after lower extremity sarcoma resection. Published data suggest that these preoperatively radiated wounds have a postoperative infection rate of 17%-44% with "traditional" dressings (e.g. dry gauze surgical dressings) [2]. A prospective series from Canada of 190 patients and showed a wound complication risk of 35% in preoperative irradiated wounds [1]. The morbidity associated with wound complications can range from moderate (prolonged dressing changes) to severe (life or limb threatening infection) [3]. The exact cause of the high rate of post-operative wound complications is not well understood.

The choice for timing of radiation is controversial [1]. However, most sarcoma surgeons favor the short term risk of preoperative radiation and its associated wound complications over higher risk of late radiation effects associated with post-operative radiation. These complications are often dose related and difficult to treat and for many patients are permanent. Extremity fibrosis, arthrofibrosis of adjacent joints, chronic edema, and fractures (that are difficult to achieve union) can be debilitating to patients. These late effects of radiation cause many treating surgeons to favor preoperative radiation.

For surgeons who must operate in an irradiated field there are several challenges. There is often a delay from the conclusion of radiation and the planned local control surgery (often between 3-6 weeks) to allow for the skin and soft tissue to recover. Despite this delay there is often evidence of soft tissue damage with skin erythema, tissue edema, and desquamation frequently observed. With large and deep tumors there is often tension on the wound edges at closure and a large amount of dead space from tissue and tumor removal. This often manifests postoperatively as a seroma which can further delay wound healing. Many of these patients will need vascularized tissue transfer for wound closure after sarcoma resection [4, 5]. This has added morbidity to the patient.

Patients who develop wound complications have been shown to longer hospitalizations and higher costs. The utilization of preoperative external beam radiation has been shown to increase the risk of postoperative wound complications [1, 6]. Anatomic location of the tumor has also been shown to be a risk factor for the development of wound complications with lower extremities being higher risk than upper extremities. There are several published studies examining the effect of negative pressure wound therapy on high risk surgical wounds. Abdominal wound complications have been shown to be reduced with the use of incisional NPWT[7]. In the orthopaedic literature the use of negative pressure incisional dressings have been shown to lower the risk of wound complications in total hip arthroplasty, ankle surgery, acetabular fractures, and extremity fractures[8-12]. Other wounds have been treated effectively with NPWT with good results include sternotomy wounds[13], cardiac surgery[14],

There are many studies published showing a significant reduction in wound complications with the use of NPWT on the surgical incision. Most published studies have demonstrated the use of NPWT to treat infections and its use for prevention is relatively novel. However, several studies have shown a benefit of incisional NPWT. Zhu and colleagues performed a retrospective chart review of 56 patients who had undergone abdominal surgical procedure. 23 patients received NPWT on the incision[7]. They showed a significant reduction in wound complications from 63.6 % to 22% (p=.02) as well as skin dehiscence (p=.014). A prospective randomized study by Stannard in high risk lower extremity fractures showed a higher relative risk of developing an infection in those not treated with NPWT (RR=1.9; 95% CI 1.03-3.55)[15]. There have been no documented complications from use of the incisional negative pressure dressing.

Recently, a Cochran Database review evaluated the use of incisional wound negative pressure therapy on closed wounds and skin grafts. There was no clear evidence that the use of NPWT improves wound healing by primary intention. There is some evidence that healing of skin grafts maybe improved with NPWT. They conclude that high quality trials are needed and should focus on wounds that are difficult to heal.[16]. Preoperatively irradiated lower extremity sarcoma wounds are ideal for such evaluation.

Following the Cochran review a systematic review was undertaken that showed included five randomized controlled trials and five observational studies on 610 patients. The literature showed a significant decrease in wound infection with the use of incisional NPWT over sterile dry dressing. No conclusion could be drawn from evaluation of other variables such as dehiscence, seroma/hematoma formation, and skin necrosis.[17]

The group of the Musculoskeletal Oncology Research Initiative (MORI) has successfully collaborated on several multi-institutional projects. This group of investigators had two poster presentation and a podium presentation at the 2013 Musculoskeletal Tumor Society Meeting in San Francisco. There are three projects in the submission phase for publication. This group consists of six executive members and twenty other musculoskeletal oncologists that are representatives of prominent academic institutions from across the country. The sites of the executive members will all participate. These sites are Stanford University, University of Iowa, Oklahoma University, Pacific Northwest University, and the Medical

University of South Carolina. Other sites may be asked to participate to ensure that the recruitment numbers are met within the enrollment period timeline.

To our knowledge, there have not been any published studies or preliminary data presented on the utility of negative pressure wound therapy in previously irradiated soft tissue sarcoma wounds. The benefits of improving wound healing in this cohort are self-evident. Reduction in major wound complications after oncologic resection of sarcomas in the setting of neoadjuvant radiation can provide improvement in quality of life, reduction in medical costs and office visits, and possibly improvement in pain and narcotic use. This high risk patient cohort could potentially benefit from reducing wound complications through NPWT and is an ideal population to study its effect. The impact of this novel and inexpensive intervention can have a profound impact on the care of sarcoma patients.

D. RESEARCH DESIGN

This study is designed as a prospective, multicenter randomized controlled pilot trial with competitive enrollment evaluating the risk of wound complications after surgical resection of extremity soft sarcomas that have undergone preoperative external beam radiation and then treated with Prevena^{TM} or standard dry gauze dressing. Six sites are planned to participate with an average enrollment of 2-6 lower extremity sarcomas eligible for inclusion each month per site.

Enrollment of subjects from each institution will be centrally regulated through the primary center, The Medical University of South Carolina. Subjects will be accrued primarily through clinic referrals to a regional musculoskeletal oncologist for evaluation of soft tissue mass. Additionally subjects may be self-referred or present to a regional referral center's hospital or emergency department. The standard of care for these patients is after a tissue diagnosis is rendered showing the mass to be a soft tissue sarcoma and appropriate staging studies are complete that the patients will receive preoperative external beam radiation. After radiation (2-6 weeks) surgery is performed for local control. The investigative portion of the study will begin in the operating room after the surgical procedure is complete. Patients evaluated who meet the inclusion/exclusion criterion (see below) will be asked by study investigators whether or not they would like to participate in this study. Informed consent for participation in the study will take place in the clinic setting (often at the time of consent for surgery) after a biopsy has shown a sarcoma and the treatment plan is to include preoperative radiation and surgical excision (which would be the standard of care). Participation will be voluntary. Patients will be randomized before or at the time of surgery to receive standard dry gauze dressing or Prevena^{TM} dressing.

Prior to or at the time of surgery the patients will be randomized to receive either a NPWT dressing or standard dry gauze dressing. This study is not amenable to blinding given the nature of dressing and the application by the surgeon. Randomization will be done by block randomization per site.

Compensation will not be provided to patients. Our goal is to obtain a total of 160 subjects with at least 6 month follow-up, approximately 75 subjects per treatment arm. (see sample size calculations)

Inclusion Criterion:
-Age>18
-Willing to consent to randomization and able to participate in the study
-Lower extremity or pelvic soft tissue sarcoma necessitating radiation prior to surgical resection
-Primary closure of wound
-Patients scheduled for surgical resection

Exclusion Criterion:
-Flap coverage or skin graft
-Patients scheduled for amputations as local control of their tumor
-Sarcomas where radiation is not planned preoperatively
-Repeat surgeries for oncologic reasons (positive margins)
-Known allergy to adhesive tape
-Recurrent soft tissue sarcoma

Consent:
Subjects will be consented for participation in the study by one of the aforementioned investigating surgeons (or research team) at the time of their evaluation in the clinic or hospital setting. Consent will include permission to randomize dressing to either to negative pressure wound therapy or "standard" dry gauze post-surgical dressing. Standardized study consent forms will be signed by the investigating surgeon and the patient. Standard surgical consent for the assigned procedure will be done in accordance with the standard of care.

Randomization:
Randomization will be predefined at each site using block randomization to ensure that each site is balanced for each arm of the study. This block randomization will be distributed and managed centrally at The Medical University of South Carolina. The randomization process will be performed centrally at MUSC and the treating surgeon will not have access to that randomization list. Preoperatively, the subjects will be blinded as to which dressing will be used for surgical wound coverage, but which dressing (i.e. which treatment arm) the patient was randomized to receive will be apparent postoperatively. Due to the design of the study, the surgeons are not able to be blinded.

Preoperative Evaluation:
Patients will receive the standard workup of a soft tissue sarcoma. The patient's preoperative evaluation or treatment plan will not be affected by this investigation or the subjects desire to participate. Data collected preoperatively will include radiation type and dose, use of chemotherapy, VAS pain score, MSTS score, PROMIS Global Health score, medical comorbidities, tumor location, and any use of pain medicines.

Operative Intervention:
Surgery will be done in accordance with the standard of care for the excision of soft tissue sarcomas. Anesthesia: Either regional or general anesthesia will be performed at the discretion of the treating physicians. Skin will closed with either staples or 2-0 nylon sutures and a temporary closed suction drain may be placed. The use and duration of the drain will be at the surgeon's discretion and in accordance with practice.

Tumor excision/limb reconstruction:
Each patient will undergo the appropriate standard of care surgical procedure regardless of which treatment arm they are randomized to. This study will not affect any of the surgical decision making or surgical technique utilized. After skin closure from the surgical procedure patients will receive either a NPWT dressing or dry gauze dressing depending on the randomization.

Postoperative Care:
Postoperative care will be identical for both treatments. Wound care instructions will be given to both groups of study patients. Instructions for the control (dry gauze) group will be within the standard of care for each surgeon's practice. Typically, a standard dressing care involves a dressing change at post-operative day two and then daily for the next week or until the wound is dry. Standardized instructions for the NPWT will be given in concordance with manufacture's recommendations. The NPWT dressing

would be typically discontinued on postoperative day 5-7 and standard dry gauze will be implemented at that point as needed. The Prevena^{TM} device is FDA approved for use on incisions.

Physical therapy will be initiated prior to discharge, and continue either at home or as an outpatient, and continued at the discretion of the therapist and treating physician and in accordance with standard practice.

Postoperative Evaluations:
Formal wound and outcome assessments will take place at the 2 week, 6 week, 3 month and 6 month visits postoperatively or if patient presents for an unscheduled office visit with a wound complaint. Some information will be gathered from the medical record such as medication usage, information about the tumor from the pathology report, days in the hospital, treatment history of the tumor, and complications. Postoperative visits, and will include recording VAS pain levels, tumor size, margin status, length of hospitalization, use of pain medicines, and functional scoring. A wound assessment will be done as well.

Wound Assessment-
Direct assessment of each participant wound will be made during the specified follow up period at 2 weeks, 6 weeks, 3 months, and 6 months postoperatively.

No validated system is designed to specifically assess surgical wounds. The CDC definition is a stringent criterion to classify surgical site infection (SSI). Infections will be classified as superficial or deep and acute or delayed. Acute infection will be defined as within 6 weeks of the surgical procedure. Delayed or late infection will be defined as greater than 6 weeks from the surgical procedure.

Criteria for wound complication (SSI or surgical site infections)-
Table 1

SUPERFICIAL INFECTION (SSSI)	DEEP INFECTION (DSSI)
Involves skin and subcutaneous tissue (and)	**Involves deep soft tissues (and)**
a) purulent drainage	**a) purulent drainage**
b) organism cultured aseptically from wound	**b) deep wound that spontaneously dehisces or is deliberately opened**
c) deliberate opening of wound	**c) an abscess or other evidence of deep infection**
d) diagnosis of SSI by attending surgeon	**d) diagnosis of SSI by attending surgeon**

Superficial infection-
Infection occurs after any operative procedure,
a*nd*
involves only skin and subcutaneous tissue of the incision
and
patient has at least one of the following:

a. purulent drainage from the superficial incision.
b. organisms isolated from an aseptically-obtained culture of fluid or tissue from the superficial incision.
c. superficial incision that is deliberately opened by a surgeon and is culture-positive or not cultured *and*
patient has at least one of the following signs or symptoms: pain or tenderness; localized swelling; redness; or heat. A culture negative finding does not meet this criterion.

d. diagnosis of a superficial incisional SSI by the surgeon or attending physician.

Deep infection-
Infection occurs after the operative procedure *and* involves deep soft tissues of the incision (e.g., fascial and muscle layers) *and* patient has at least one of the following:
a. purulent drainage from the deep incision.
b. a deep incision that spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or not cultured *and* patient has at least one of the following signs or symptoms: fever (>38°C); localized pain or tenderness. A culture-negative finding does not meet this criterion.
c. an abscess or other evidence of infection involving the deep incision that is found on direct examination, during invasive procedure, or by histopathologic examination or imaging test.
d. diagnosis of a deep incisional SSI by a surgeon or attending physician.

Risks Associated With NPWT Therapy/Dressing

Risks Due to PREVENA ™ Incision Management System

Risks	Disorders/Conditions
Skin and Subcutaneous Tissue	• Local cutaneous reaction (i.e. redness, rash, significant pruritis, urticaria) • allergic reaction • maceration • minor soft tissue damage • epidermal (skin) stripping • minor bleeding • pain • contusion (bruising)
Other	• bleeding complications (associated with the surgical procedure, concomitant therapies and co-morbidities) • first degree burn (if device gets warm) • exposure related infection • localized infection • physical discomfort • minor desiccation (due to dressing leak) • moderate soft tissue damage (i.e. due to trip hazard, tubing entanglement) • deterioration of the wound (due to lack of visibility of incision site through dressing)

E. METHODS

Table 2

ASSESSMENT Provena™ 1 week duration	PRE-OP	2 WEEK POST OP VISIT	6 WEEK POST OP VIST	3 MONTH POST OP VISIT	6 MONTH POST OP VISIT
Wound assessment		X	X	X	X
Tumor size (cm)		X			
Type and Dose of Radiation	X				
Margin (+/-)		X			
Pain (VAS)	X	X	X	X	X
Hospitalization (days)		X			
Narcotic usage (+/-)	X	X	X	X	X
MSTS score			X	X	X
PROMIS Global Health	X			X	X

Other data collected to be analyzed for an association with wound complications or impact on treatment effect of Prevena™ (table 2)-

1) Surgery associated wound healing factors- prolonged (>3 wks) drainage, need for prolonged dressing changes or wound packing (>3 wks), return to OR, and use of antibiotics- All visits
2) Size of the tumor resected (cm)-2 week visit
3) Development of postoperative hematoma or seroma- All visits
4) Patient comorbidities- Smoking, peripheral vascular disease, BMI, diabetes, and MRSA status
5) Pain: The subject will be asked to record their current level of leg pain, and level of pain with leg use on a visual analogue scale (VAS) at all visits
6) Length of hospitalization (days)-2 week visit
7) Duration of narcotic usage (days)-All visits
8) Physical Function: The subject will be asked to complete a MSTS score, a validated patient survey for assessment of function at the 6 week, 12 week, and 6 month
9) Patient Global Assessment: The subject will be asked to complete a PROMIS Global Health forma validated patient survey for assessment of global musculoskeletal health and wellbeing at the preoperative visit, 3 month and 6 month visits.

Adverse Events:
Definitions
Adverse Event (AE).
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including clinically significant abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

This definition includes events:
- related to the study device or the comparator,
- related to the study procedures involved,
- resulting from user error or from intentional misuse of the study device.

Serious Adverse Event(SAE)
An adverse event is considered serious if it results in any of the following outcomes:
- Death
- A life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

Unanticipated adverse device effect (UADEs)
A UADE is any SAE on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death 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)

Expectedness
All Serious Adverse Events will be assessed for expectedness based on the following definitions:

Expected, Anticipated: the effect, problem, or death had been previously identified in nature, severity, or degree of incidence in the study or product documentation.

Unexpected, Unanticipated: if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study or product documentation

UADE Reporting to KCI, USA Inc.
UADEs and SAEs must be reported by the Investigator to KCI and the reviewing Institutional Review Board (IRB) per their reporting requirements.

Secondary analysis will include oncologic specific outcomes- local recurrence and distant relapse.

Coordination of all sites:
Data will be stored on the MUSC RedCAP database system. Protocol information such as unanticipated problems, adverse events, findings that change risks to patients, confidentiality loss, changes to protocol, and interim analysis findings will be discussed at monthly conference call meetings of all coordinating investigators.

Data Management:
All paper data will be stored at the clinical sites in locked file cabinets in compliance with institutional and federal policies for the storage of personal health information. Electronic data will be stored on the institutional protected hard drive. Study specific data such as survey results will not be made part of the

patient's permanent electronic medical records. Only study investigators will be given access to these files. Data will be stored on the institutional REDCap database. Patients from all sites will be given unique identifiers prior to input into REDCap.

Data safety and monitoring will be completed by the Principle Investigator. The PI will review and report any adverse events, protocol deviations/violations, early stopping rules and internal audit results. In addition to the oversight of data safety the PI will be responsible for identifying, reviewing monthly, and reporting adverse events. Data from other institutions will be reviewed by the study team and PI on a semi-annual basis.

Statistical Considerations: Statistics will be managed through MUSC Biostatistics core.
Analytic Approaches: To assess specific aim one patients will be followed longitudinally for the development of a wound complication and incidence of secondary procedures. Criteria for a wound complication are listed above. The data will be collected prospectively during routine follow up care of the patient and will include presence of absence of wound complication. The proportion of patients with a wound complication will be estimated and the 95% confidence for the true wound complication rate will be calculated with an exact binomial procedure. Although it is not the primary analysis, we will also compare the complication rates across the two groups using a Fisher's exact test (although the study is underpowered for this analysis). We will also use a logistic regression analysis where we adjust for center (using indicator variables) to estimate the overall wound complication rate in each group. For the risk of secondary interventions, the incidence of procedures performed for wound complications will be collected and multiple logistic regression analysis will be used to adjust these procedures in the incidence of wound complications.

To assess specific aim two the total cost of perioperative and post-operative care will be estimated from hospital billing records for patients. The median cost for the NPWT group and control group will be estimated and compared with independent t-test for normally distributed data and the Mann-Whitney test for any nonparametric data. A post hoc analysis of the cost of treatment for each arm will provide comparative effectiveness data for the use of NPWT in preoperatively radiated sarcoma surgical wounds. This is come directly from hospital and clinic charges, dressing and medication costs, and direct societal cost estimates from time missed from work.

Sample size justification: This is a pilot study with the primary objective of estimating complication rates in our patient population using NPWT and traditional dry dressings. We estimate that each of four institutions can enroll a least 40 patients over 36 months for a total of 160 patients. Assuming up to 5 patients in each group will have inevaluable data or follow-up, we plan on a total of 75 evaluable patients in each group. With 75 patients in each group and assuming complication rates of 10% to 30%, we have the following ½ widths for 95% confidence intervals.

Table 3: Precision of estimates of wound complication rates based on a sample size of 75 for observed complication rates ranging from 11% to 30%.

Observed wound complication rate (N=75)	95% Confidence Interval	Half-width of 95% confidence interval
11%	(4.7% , 20.0%)	7.6%
15%	(7.6%, 24.7%)	8.6%
20%	(11.6%, 30.8%)	9.6%
25%	(16.0%, 36.7%)	10.4%
30%	(20.5%, 42.4%)	10.9%

References:

1. O'Sullivan, B., et al., *Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial.* Lancet, 2002. **359**(9325): p. 2235-41.
2. Kunisada, T., et al., *Wound complications following pre-operative radiotherapy for soft tissue sarcoma.* Eur J Surg Oncol, 2002. **28**(1): p. 75-9.
3. Tseng, J.F., et al., *The effect of preoperative radiotherapy and reconstructive surgery on wound complications after resection of extremity soft-tissue sarcomas.* Ann Surg Oncol, 2006. **13**(9): p. 1209-15.
4. Barwick, W.J., et al., *Vascularized tissue transfer for closure of irradiated wounds after soft tissue sarcoma resection.* Ann Surg, 1992. **216**(5): p. 591-5.
5. Peat, B.G., et al., *Wound-healing complications after soft-tissue sarcoma surgery.* Plast Reconstr Surg, 1994. **93**(5): p. 980-7.
6. Davis, A.M., et al., *Function and health status outcomes in a randomized trial comparing preoperative and postoperative radiotherapy in extremity soft tissue sarcoma.* J Clin Oncol, 2002. **20**(22): p. 4472-7.
7. Zhu, F.J., *[Thirty-eight cases of abdominal incisional fat necrosis after gynecologic operation treated with moxibustion].* Zhongguo Zhen Jiu, 2012. **32**(8): p. 683-4.
8. Stannard, J., *Complex orthopaedic wounds: prevention and treatment with negative pressure wound therapy.* Orthop Nurs, 2004. **23 Suppl 1**: p. 3-10; quiz inside back cover, back cover.
9. Stannard, J.P., et al., *Negative pressure wound therapy after severe open fractures: a prospective randomized study.* J Orthop Trauma, 2009. **23**(8): p. 552-7.
10. Hansen, E., et al., *Negative pressure wound therapy is associated with resolution of incisional drainage in most wounds after hip arthroplasty.* Clin Orthop Relat Res, 2013. **471**(10): p. 3230-6.
11. Goldstein, J.A., et al., *The use of negative pressure wound therapy for random local flaps at the ankle region.* J Foot Ankle Surg, 2010. **49**(6): p. 513-6.
12. Reddix, R.N., Jr., et al., *Incisional vacuum-assisted wound closure in morbidly obese patients undergoing acetabular fracture surgery.* Am J Orthop (Belle Mead NJ), 2009. **38**(9): p. 446-9.
13. Atkins, B.Z., et al., *Does negative pressure wound therapy have a role in preventing poststernotomy wound complications?* Surg Innov, 2009. **16**(2): p. 140-6.
14. Colli, A. and M.L. Camara, *First experience with a new negative pressure incision management system on surgical incisions after cardiac surgery in high risk patients.* J Cardiothorac Surg, 2011. **6**: p. 160.
15. Stannard, J.P., et al., *Incisional negative pressure wound therapy after high-risk lower extremity fractures.* J Orthop Trauma, 2012. **26**(1): p. 37-42.
16. Webster, J., et al., *Negative pressure wound therapy for skin grafts and surgical wounds healing by primary intention.* Cochrane Database Syst Rev, 2012. **4**: p. CD009261.
17. Ingargiola, M.J., L.N. Daniali, and E.S. Lee, *Does the application of incisional negative pressure therapy to high-risk wounds prevent surgical site complications? A systematic review.* Eplasty, 2013. **13**: p. e49.