Research Project Proposal
Submission to: MPP Research Fund

Project Title


Principal investigator
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April 19, 2018
Title:

Trial Registration:
The trial will be registered on the NIH trial registration website “www.clinicaltrials.gov”

Research Team:

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Roles and Responsibilities:
Authors’ contributions:
Study conception: Eman Sbaity, MD; Jamal Hoballah, MD
Study design: Eman Sbaity, MD
Implementation: Jamal Hoballah, MD; Mohamad Khalifeh, MD; Eman Sbaity, MD
Grant Holders: Eman Sbaity, MD
Statistical Analysis: Eman Sbaity, MD
Refinement and Approval of the Study Protocol: Eman Sbaity, MD; Jamal Hoballah, MD; Ghada El-Hajj Fuleihan, MD; Elie Akl, MD

Time Commitment:
% Effort Commitment to the Project per Investigator:
Eman Sbaity, MD, the lead PI (10% effort)
Both co-investigators will spend 5% of their time on this proposal
I. Abstract:

Background:
Wound complications following midline laparotomies are common and are a main source of postoperative morbidity including superficial or deep wound infection, skin dehiscence, fascia dehiscence, and incisional hernia. Abdominal closure complications are strongly associated with suture technique and material, in addition to other factors related to the patient and type of surgery performed. The traditional technique is to place the fascia sutures 1 cm apart and at least 1 cm away from the fascia edge. A Swedish study described a new technique placing the sutures closer to each other and closer to the fascia edge, resulting in lower rate of abdominal wound complications. This study has a number of limitations preventing adopting its results.

Rationale:
There is a need for better quality evidence to convince the surgical community to change closure technique of abdominal wounds aiming to improve morbidity. The primary objective of the COFACTOR study is to compare incidence of incisional hernia one year postoperative in patients undergoing elective midline laparotomies using the new versus conventional closure techniques. Secondary outcomes include various wound complications and QOL.

Methodology:
This is a 1:1 randomized, controlled, patient and assessor blinded, parallel design, superiority trial, with primary endpoint of incisional hernia at one year. The study will be conducted at AUBMC over a three year period. Patients planned for a non-emergent midline laparotomy for a general surgery or vascular procedure will be randomized to either technique of fascia closure. In order to detect a drop of 12 % in incidence of incisional hernia, with an alpha of 5% and 90% power, we will need to recruit 27 patients in each arm. After adjusting for loss to follow up, target recruitment is 78 subjects. We will compare both arms for the primary, secondary, and exploratory outcomes, using chi-square or t-test as appropriate. Univariate and Multivariate logistic regression will be done.

Significance:
The results of this study will allow surgeons to assess the role of a new abdominal closure technique in decreasing short and long term postoperative complications, for a commonly performed procedure. This trial will generate evidence-based conclusions.
II. Background and Rationale:

Wound complications following midline laparotomies are common and are a main source of postoperative morbidity and increased length of hospital stay (1). Postoperative morbidity includes a spectrum of superficial or deep wound infection, skin dehiscence, and fascia dehiscence with or without evisceration. In addition, incisional hernia is a common delayed postoperative complication occurring in 9-26% of patients undergoing midline laparotomies (2,3). Fascia dehiscence is a major complication that presents either early with evisceration or late with incisional hernia (2,3). Most patients with fascia dehiscence undergo a second surgery for fascia closure, which by itself is associated with morbidity and a high recurrence rate (1).

Abdominal closure complications are strongly associated with suture technique and material, in addition to other factors related to the patient and type of surgery performed. A 2010 survey among surgeons found no consensus with regards to the best technique to close the laparotomy incision (4). Many RCTs and systematic reviews of the optimal technique to close the abdomen have been reported with heterogeneous results. A recent meta-analysis of 14 trials found significantly lower hernia rates using a continuous versus interrupted suture technique with odds ratio (OR) of 0.59 (95% confidence interval (CI) 0.43, 0.82), and with slowly absorbable versus rapid absorbable suture material with OR: 0.65 CI (0.47, 0.9) (5). Thus, there is adequate evidence for using continuous suture of a slowly absorbable material to close the abdominal midline incision. However, the technique of performing the continuous suturing is not adequately studied. The traditional way performed by most surgeons is to place the fascia sutures 1 cm apart and at least 1 cm away from the fascia edge.

A group of surgeons from Sweden described a new technique placing the sutures closer to each other and closer to the fascia edge. The aim is to have a ratio of 4:1 between the overall lengths of the suture to the length of the wound being closed (6). The authors conducted a randomized controlled trial of 737 patients, where 381 were allocated to the conventional technique arm with wide stitches and 356 were allocated to the new closure technique arm with short stitches. They recruited patients who underwent midline laparotomies for emergency or elective indications. Patients with a previous midline incision, or a preexisting ventral hernia such as an umbilical or epigastric hernia were not eligible. Their results showed lower incidence of wound infections, dehiscence, and incisional hernias with their new fascial closure technique as compared to the conventional one. Outcome measures were defined and assessed clinically. They only assessed fascia dehiscence requiring reoperation.

The Swedish study had a number of limitations (6). The allocation method was a pseudo-randomization rather than a true randomization of the study participants. Patients undergoing laparotomies in one week were allocated to one treatment arm and those undergoing laparotomies in the following week were all allocated to the other treatment arm. This is an old and obsolete randomization strategy. Another limitation is lack of standardization of the suture size: they used 1-0 loop PDS sutures in the conventional
Closure technique and 2-0 loop PDS sutures in the short and close suturing technique. The authors vaguely described how they did their measurements to ensure proper distances and suture lengths. The study population was not well described where much information about comorbidities and risk factors of dehiscence are not reported in their paper. This makes it difficult to comment on generalizability and patient eligibility for the new technique. The authors included both elective and emergency operations which will cause heterogeneity of the results since emergency cases are more prone to develop abdominal wound complications. In addition, the authors did not clarify whether they implemented established guidelines intended to prevent surgical site infection (SSI), where SSI is a major risk factor for failure of abdominal closure and consequent dehiscence or incisional hernia. Non-compliance with these guidelines in their practices would confound the results (6). Thus this study provides low quality evidence. Despite its limitations, this study presents interesting results and a potential for decreasing complication rates for a commonly performed procedure.

There is a need for better quality evidence to convince the surgical community to implement changes in their closure technique of abdominal wounds. We propose to conduct a randomized controlled trial that addresses the limitations in the design of the existing trial and that will help establish superiority of the new technique. In this trial, we will compare closure of abdominal wounds in patients undergoing midline laparotomy incision using:
1. Traditional closure technique, with placement of sutures at least one cm away from the fascial edge and one cm apart from the adjacent fascial suture.
2. Alternative closure technique using smaller and closer fascial sutures, with placement of sutures only 5 mm away from the fascial edge and 5 mm apart from the adjacent fascial suture.

III. Hypothesis
Closure of abdominal fascia in elective midline laparotomy incisions with small and close fascial sutures compared to closure with conventional wide and distant fascial sutures results in lower rates of fascial dehiscence, incisional hernia, and wound infection, and improved quality of life.

IV. Objectives
The primary objective of the COFACTOR study is to determine the relative effects of new versus conventional closure techniques on incisional hernia one year postoperative in patients undergoing elective midline laparotomies.
The secondary objectives of the trial are to determine changes in the rates of fascia dehiscence and evisceration within 30 days and the rates of intervention for wound complications in subjects randomized to the new closure technique with short and narrow sutures.
V. Methods:

Trial Design:
This trial is designed as a 1:1 randomized, controlled, patient and assessor blinded, parallel design, superiority trial, with primary endpoint of incisional hernia at one year.

Study Settings:
We will conduct the study at the American University of Beirut Medical Center, which is an academic, tertiary referral center.
Prior to conducting this trial, we will conduct a pilot study to study feasibility of implementing the final trial by assessing items related to the institutional systems, the trial itself, and study subjects. The pilot study will assess patient’s response rate to participate in the trial, acceptance of patients to be examined daily by the research team, adherence of patients to the scheduled postoperative visits especially the one year follow up visit, and proportion of loss to follow up. In the pilot we will also study compliance of research assistant with conducting the required measurements, the reliability of the randomization and allocation concealment strategy, and success of blinding of the research team from treatment allocation.
In addition, the pilot study will study efficacy of the training session and procedure video, consistency of evaluation among different surgeons and radiologists performing the outcome assessments, and adequacy of the study team to be available for the scheduled evaluations.

Eligibility Criteria:

Surgeons Eligibility:
General and Vascular surgeons who want to enroll their patients into the trial have to be familiar with the new fascia closure technique. They have to attend a presentation given by the study principal investigator explaining the details of the new investigational procedure and watch a video demonstrating the new technique during the presentation. At AUBMC, the fascia is typically closed by the surgeon or a senior surgical resident either postgraduate year 4 or 5. Procedures performed during the pilot phase will count towards the final number of procedures requested for the trial.

Subject Eligibility:
Inclusion Criteria:

1) Age 18 years or older
2) Signed Informed Consent
3) Undergoing an elective laparotomy through a midline incision
Exclusion Criteria:
1) Emergency surgery
2) Laparotomy through an incision other than midline
3) Previous midline laparotomy
4) Presence of incisional or ventral hernia at time of laparotomy
5) Incisional hernia repair
6) Laparotomy surgery during pregnancy

Interventions:
The first group will undergo traditional closure with wide and distant sutures, where each suture is placed at least one cm away from the fascia edge and one cm apart from the adjacent fascia suture.
The second group of patients will undergo the alternative closure with small and close fascia sutures, where each suture will be placed only 5 mm away from the fascia edge and 5 mm apart from the adjacent fascia suture.
In the first group, an average of one suture will be placed at each cm length of the wound, thus the number of sutures placed should be equal to the length of the wound in cm. In the second group, an average of two sutures will be placed at each cm length of the wound, thus the number of sutures placed should be equal to at least double the length of the wound in cm.

Strategies to improve adherence to intervention protocol

The length of the fascia incision will be measured just before the surgeon starts the closure and this measurement will be documented or research assistant in the operating room. After the wound is closed, the remaining suture length is measured again and documented as well. For a successful closure of the wound with this new technique, the utilized suture length should be 4 times the length of the wound. Approximately an additional 10 cm of suture length is needed to ensure proper tying of the knot after conclusion of the suturing. The remaining suture length should reflect these two considerations. The surgeon or chief resident will independently calculate the used and remaining suture length. The formula will be as follows: [Original Length of Suture (Length of suture remnants at the starting knot + Length of suture remnant at the finishing knot)] / Length of the skin incision. If the final calculation result doesn’t reflect the planned 4:1 ratio between the suture length and wound length, then the patient has to be removed from the study.
If a surgeon fails to ensure the 4:1 closure technique on 3 patients then his patients cannot participate in the trial or he has to attend the lecture on technique, watch the demonstration videos, and get proctored again on 3 cases, before he can resume participating in the trial.
During the duration of hospital stay, it is the responsibility of the PI/study team to ensure proper and timely assessment of outcome measures, including timely visits by the surgeon evaluator. Upon discharge from the hospital, the patients will be given a calendar as timeline chart on the dates of the remaining follow up dates. The study team will call the
patients one week and 48 hours before the 30 day appointment and two weeks and one week before the one year appointment to ensure they will show up.

**Relevant concomitant care and interventions during the trial:**
Closure of the subcutaneous tissue and skin will be left at the discretion of the treating surgeon, since currently there is no definitive evidence on the optimal methods following a laparotomy.
Whether to placing regular or closed suction drains or not in the subcutaneous tissue is also left to the discretion of the treating surgeon, since there is no consensus on this topic in the surgical literature.
Postoperative care of the patient during hospitalization and throughout the duration of the study will be performed according to usual care adopted by each surgeon, thus this care will vary by surgeon and indication of surgery.
Measures to prevent wound infections will be done following the hospital policy derived from the CDC guidelines on prevention of surgical wound infections. Wound infection will be managed according to the general principles of skin opening and antibiotics.

**Outcomes:**

**Primary Outcome Measures:**

- Incisional hernia at 12 months:
  We will define incisional hernia according to the European Society of Hernia: “any abdominal wall gap with or without bulge in the area of a postoperative scar perceptible or palpable by clinical examination or imaging”. (7) Using both clinical exam and imaging if performed, these hernias will be described according to their location along the midline, size of the defect using vertical and transverse measurements, and reducibility of any protruding viscera upon lying down or following gentle pressure by the examining hand. Also, we will collect information whether the hernia is causing any pain, discomfort, decrease in mobility, or any incidence of incarceration where the hernia contents protrude and does not reduce to the abdomen upon gentle pressure.

**Secondary Outcome Measures:**

- Fascial dehiscence or evisceration within 30 days:
  Fascial dehiscence is defined as gapping of the fascia by at last 1 cm with loosening of the surgical sutures. This presents initially with increased serous fluid drainage from the wound. This may be self-limited or progress to a wider gap with herniation of the abdominal viscera, usually the small bowel or the greater omentum, through the defect. The excessive fluid drainage results in opening of the superficial skin incision in some patients and this necessitates emergency surgery for repeat closure of the abdominal wall.

- Intervention rate for wound complications at 30 days postoperative:
  Intervention includes incision and drainage for a wound infection, evacuation of a hematoma, aspiration of a seroma, or reoperation for a wound dehiscence.
Exploratory Outcomes:

- Wound seroma within 30 days postoperative:
  - Wound seroma defined as collection of serous fluid in the subcutaneous space, detected either clinically or by ultra-sound examination.
  - Wound seroma is an established risk factor for wound infection and further resultant morbidities.
- Wound infection within 30 days postoperative:
  - Wound infection will be defined according to the Centers of Disease Control CDC criteria for Surgical Site Infection SSI. (Appendix A)
  - Wound infection is a well known cause of fascia dehiscence. In addition, fascia closure technique resulting in fascia ischemia will result in deep surgical site infection, which in turn can lead to fascia dehiscence. The Sweden group believe that the wide fascia bite result in higher risk of fascia ischemia and thus delayed fascia healing or higher risk of deep wound (fascia) infection and higher risk of fascia gapping.
- Pain during hospitalization:
  - Pain will be measured using “0–10 Numeric Pain Rating Scale” (8) (Appendix B) on POD 1, POD 7, and on discharge (if the patient stays less or more than 7 days). The research assistant will collect information on pain killers given to the patients postoperatively. This information will be taken into consideration when assessing pain ratings.
- Quality of Life (QOL) at 12 months:
  - QOL will be measured using Short Form SF-36 questionnaire (Appendix C), which has been validated in the Arabic language (9)

Participant Timeline:

Enrollment:
After the primary attending introduces the study to the patients in the outpatient clinics or in the hospital during their admission period before surgery is performed, the research assistant will approach the patient and discuss the research study with them.

Assessments and Visits:
Daily visits to the participants will be conducted by the surgeon evaluator while in the hospital for the first 7 days to evaluate relevant outcome measures. The surgeon evaluator will examine the wound for possible complications including seroma, hematoma, collections, or fascia gapping. The last evaluation will be on day 7 postoperative or on the day of discharge if the postoperative length of hospital stay was shorter or longer than 7 days.

A similar clinical assessment will be done at 30 day postoperative, with a range of -7 and +7 days. Discharged patients will be asked to present to the outpatient clinic for the 30-day assessment. Patients remaining hospitalized at 30 days will be visited by the surgeon evaluator.
Two or three independent surgeon evaluators will be identified at our center to perform the clinical evaluation. The surgeon evaluator will be either a general surgeon or a vascular surgeon willing to dedicate time for the trial. She/he can't be the attending physician of the study subject. They will receive the training session with the remaining faculty who will enroll patients on the trial.

The research assistant on the study will perform pain assessment on postoperative day 1 and 7 and at the 30-day postoperative visit.

Twelve months after surgery, the subject will come to outpatient clinic for clinical evaluation of the wound for evidence of incisional hernia and administering the quality of life (QOL) questionnaire. This is done with a range of +/- 30 days. In case the patient cannot reach to clinic due to disability or difficult accessibility, then the surgeon evaluator will administer the QOL questionnaire through the phone.

**Sample Size:**
Millbourn et al compared long to short continuous stitches and found a drop in incisional hernia rate at 1 year from 18 to 6% and a drop of SSI from 10 to 5% (6). In order to detect a drop of 12% in incidence of incisional hernia, with an alpha of 5% and 80% power, we will need to recruit 20 patients in each arm. We need 27 patients per arm to detect this difference with 90% power, and a total of 54 patients in the trial. We are expecting a 30% loss to follow up, so our adjusted target recruitment will be 78 subjects in total.

**Recruitment:**
Possible candidates will be identified from surgery outpatient clinics during the preoperative visit. The attending surgeon will introduce briefly the trial to the patient, and if the patient agrees to participate, he will be approached by the research assistant. If a candidate was not approached in clinic, the RA will approach them prior to surgery, only after the attending physician gets the patient approval.

The expected recruitment rate is 1-2 patients per week. Consequently, it will take about one and a half years to recruit a total of 78 patients. At AUBMC, we currently perform 300 open laparotomies per 12 months. This recruitment rate will be tested in the pilot phase of the study.

Patients will be reimbursed for transportation and parking fees to cover their trips to our clinics for outcome assessments.

**Assignment of interventions**
**Sequence Generation:**
Participants will be randomly assigned to their treatment in a 1:1 ratio, according to a computer generated schedule, stratified by type of surgery (vascular or non-vascular), using permuted blocks of variable sizes.
**Allocation Concealment Mechanism:**
Random sequence generation will be selected by CRI biostatistician using computer software. The CRI person will hold details of the blocking and block sizes in a separate document unavailable to those involved in the study including those enrolling patients, collecting data, evaluating outcomes, or analyzing data, so we ensure concealment. The CRI person will not share the treatment intervention with study personnel until baseline characteristics are collected, and patient is recruited into the trial. The day before the surgery, the surgeon will contact the CRI biostatistician and receive treatment allocation, so he or she can perform the fascia closure technique to which the patient is randomized to.

**Implementation:**
A CRI biostatistician, who is not involved in this study, will generate the randomization sequence and keep hold of it. The participants will be recruited and consented by the research assistants based on eligibility to join the study without any knowledge about their allocation arm. The day before the surgery, allocation will be revealed by the biostatician to the treating surgeon to perform the fascia closure. However, none of the study team will be informed about the treatment allocation.

**Blinding (Masking):**
It is impossible to blind the operating surgeon to the allocation, but the rest of the study team will be blinded. We will blind to allocation the surgeon evaluator who will assess for outcomes, data analysts, the surgical team taking care of the patient (excluding the operating surgeon and residents on the case), and patients themselves. The operating surgeon and residents on the case are strongly instructed not to disclose allocation status to any of the study team or the patient. The 2 closure techniques will be referred to and entered in data sheets as A and B, without knowledge of what A or B are.

If wound complications occur that necessitates reoperation for fascia dehiscence then the closure technique will be left to the discretion of the operating surgeon.

**VI. Data collection, management, and analysis**

**Data Collection Methods:**
Data on basic demographics of the study subjects, relevant risk factors, confounders, and indication for laparotomy surgery will be collected at baseline using protocol specific standardized case report forms, CRF. These will be developed to reflect the eforms that will be developed for the protocol. The CRF will be completed by the research assistant, following informed consent and prior to the surgical procedure. Data will be collected directly from the patient. The lead investigator will train the research assistants to properly fill the CRF. Surgeons involved with the outcome assessment will attend a presentation detailing the definitions of the different outcomes and discuss the standardized measurement procedure. A pilot study will be conducted prior to launching the trial. In the pilot study, all surgeon evaluators will independently assess the outcomes of the subjects included in the
pilot study till 30 days. Inter-rater reliability will be measured. In case of inconsistency of results, the reasons behind the discrepancy will be investigated and addressed by redefining the outcome measures, clarifying measurement techniques, or further training. Consistency of evaluation among different surgeons will be evaluated in the pilot phase.

The different sections of that data will be collected at the different points in time of the study by questionnaires administered by the study research assistant to the patient. Evaluators are requested to fill immediately a case report form each time they perform an outcome evaluation on a study subject. These forms will be handed in the same setting to the research assistant who will take care of storing them.

The research assistant will check the pain score using “0–10 Numeric Pain Rating Scale”. QOL data will be collected using the validated Arabic version of the Short Form SF-35.

To improve retention and compliance with the one year follow up, we will contact the patient ahead of time, and compensate them for transportation and parking. We will make sure the allocated times for the research visits are available at different times during the day and at a different days of the week, including few slots on Saturday for those who cannot make it during the week.

When a patient fails to comply with the follow up exams, we will collect applicable data on the phone. For those who drop from the study, we will get their permission to contact them by a phone call one year post their surgery to check whether they developed a clinically detectable incisional hernia and if they had any surgery for the hernia.

**Data Management:**

The research assistant will enter the data from the Case Report Forms on the study data excel sheet within one week of its collection. Clear explanation of all headings and variables in the data collection sheet will be done on a separate word document for future reference. Coding of the data will be clarified from the start on a separate sheet within the same document. The data will be manually entered twice and independently by the research assistant and another member of the study team. Data will be entered as the actual numeric values or the actual categorical variable, initially. In the end, the statistician will code all the data in preparation for analysis. The PI will perform spot checks on the data and will review weekly all the CRF and assessment collection sheets performed within each week.

The principle investigator plans a weekly meeting with the research team to raise and discuss any issues related to data collection, missing data, and retention of patients.

We will have a password security protected laptop for the research assistant. At AUBMC, data will be stored on the AUB intranet server. The Case Report Forms will be stored in a locked cabinet in the PI or lead investigator office 3 years following publication of study results. We will provide a SOP (standard operating manual) detailing data management procedure to ensure consistency in case of change in the study members.
Audits will be performed monthly on 20% of the charts.

**Statistical Methods:**

The intervention arm (short and narrow stitches) will be compared to the standard arm (long and wide stitches) for the primary, secondary, and exploratory outcomes. We will use the chi-square or Fischer exact test if the expected count of any of the outcomes is less than 5 per cell for analysis of incidence of dichotomous outcomes (fascia dehiscence, incisional hernia, wound seroma, wound infection, and intervention for wound complications). We will use independent t-test for analysis of the continuous outcomes (pain score, and QOL measurement). We will calculate relative risk with corresponding 95% confidence intervals to compare incidence of the dichotomous outcomes and we will report difference in means for the continuous outcomes. SPSS version 20 will be used to conduct the analysis. A 2 sided p-value will be set at 5%.

Univariate analysis will be performed separately for the primary outcome and the two secondary outcomes. Univariate analysis will be conducted separately incisional hernia at one year, intervention for wound complications at 30 day postoperative, and dehiscence at 30 days postoperative as the dependent variable and vascular indications, diabetes status, BMI, incision length, wound classification (clean, clean-contaminated, or contaminated) and operating surgeon as the independent variables. BMI will be categorized as normal, overweight, obese, and morbidly obese according to consensus BMI values cutoffs for these definitions (Appendix D- Definitions). Wound status will be classified according to ACS wound classification system (Appendix D- Definitions).

Multivariate analysis using logistic regression will be performed looking at how the primary outcome and each of the secondary outcome measures are affected by each of the above listed 4 covariates. We will perform subgroup analysis for the primary and secondary outcomes using chi-square according to the following variables: operation for vascular vs. non-vascular disease; obese vs. non-obese patients. We anticipate that in the obese patients, the seroma and wound infections will be significantly less in the intervention versus the standard group. We anticipate that the improvement in primary outcomes, especially in incidence of incisional hernia at one year will be more pronounced in the vascular surgeries.

We will perform both intent-to-treat and per-protocol analysis for all outcome measures. The intent-to-treat analysis will include all patients in the arm to which they were randomized. Multiple imputation methods will be used to handle missing data. To assess the effect of missing data on the analysis, sensitivity analyses will be performed. The study biostatistician will perform best case scenario, worst case scenario, and group averages. For outcome measures missing from the 30 day assessment but available at discharge from the hospital, the biostatistician will use approach of “last observation carried further”. We will assess the baseline characteristics of those who will be lost to follow up, to help us understand what the potential outcomes were.
VII. Data Monitoring

Data monitoring Committee (DMC):
The DMC committee will be independent of the principal investigator and the funders of the trial. It will be composed of a surgeon, an internist, one nurse, a biostatistician, and a representative from the patient advocacy office at AUB-MC. The surgeon will be either a general or vascular surgeon. The internist will have a clinical research background, and if possible an administration background. The nurse will be picked from the internal medicine floors or outpatient clinics, to make sure they are not taking care of any of the study patients. All members should not have any conflict of interest related to the study. The DMC will be chaired by the internist, who has to keep a record of the meetings and recommendations for future reference. Since this is an investigator-initiated trial, the principal investigator will appoint the DMC members.

The DMC will meet every other month, at times of scheduled interim analysis, and upon conclusion of the study. The primary role of the DMC is to review accumulating data and alert the steering committee if there are alarming rates of side effects in any arm of the trial. This committee doesn’t have executive power to stop the trial or modify treatment. It will report results to the steering committee which will then decide on the fate of the trial. In addition, the DMC will keep track of accrual rate.

Interim Analysis:
The interim analysis will be done 3 times throughout the study; upon recruiting quarter, two-quarters, and three-quarters of the study population. The study biostatistician who is blind to the treatment allocations will conduct the interim analysis and will use the O’Brien Fleming stopping rules. The study biostatistician will report results of the interim analysis to the DMC confidentially. At each interim-analysis interpretation, the DMC will alert the steering committee if one arm is found to be beyond doubt either more beneficial or more harmful than the other arm. The PI will take in consideration the results of the interim analysis, opinion of the DMC, and various important factors to decide upon the fate of the trial. The chairperson of the DMC will monitor the clinicaltrials.gov website for registration of new trials and for newly reported results from trials addressing similar question as this trial.

Harms:
The adverse effects can be part of the outcome measures we detailed earlier in the protocol or other not specified side effects. Either way, any side effect will be reported and the subject will be managed according to the standard of care or the preference of the treating surgeon.

Auditing

The PI will schedule a weekly meeting with all the study members to review eligibility of new participants enrolled in the study, consent forms, all case report forms (CRFs), all
assessment sheets filled during that week, adherence to trial interventions and policies, and reports of side effects. The PI will double check the entered data in terms of completeness, timeliness of entry, and correctness of the data. Random checks will also be done.

VIII. Ethics and Dissemination

Research Ethics Approval:
We will submit this protocol, informed consent template, case report forms, and other study related appendices to the Institutional Review Board (IRB) at each of the study sites to review the scientific soundness of the project, ethical aspects, and its impact on medical practice for our patient population. The PI will submit progress reports to IRB annually from the date of the first IRB approval and within a month of study completion and later upon termination.

Protocol amendments:
Any modifications to the protocol regarding study objectives, study design, eligibility criteria, sample sizes, or significant changes in the study that will impact study conduct, potential benefit or safety of the study subjects will initially require agreement from the research study steering committee. Then the amendment will be submitted to the IRB for approval before implementation. The study participants will be notified of study changes and will sign an updated informed consent form reflecting such changes.

Consent:
After the primary surgeon introduces the study to the patient, the research assistant will explain the study and invite the patients to sign the consent form. The research assistant will be trained by the principal investigator on the process of signing the consent. In addition, other members of the study team will be trained and certified to obtain the consent, so they can help in case the research assistant was not available to discuss participation with a potential candidate. The subject will be given opportunity to ask questions regarding the study and will receive a copy of the IRB approved and updated consent form (CF) with his/her signature.

Confidentiality:
All study related forms and information will be stored at each study site, where they are stored in cabinets that can only be accessed by study members. All electronic databases will be password protected. Computers used during this study will also be password protected.

Declaration of interests:
The study team members do not have any financial, academic, or personal conflict of interest to disclose.
Access to data:
The steering committee will have access to the data while the study is in progress. At conclusion of the study, principal investigators and co-principal investigators will have full access to the identified data.

Dissemination policy:
All data and analysis will remain blinded until main outcomes are published. The study results will be communicated to the participants by email, letter by mail, or a phone call by the PI.
We will submit a de-identified dataset to an appropriate data archive after 3 years of study termination to share our data with the surgical community.

Authorship
To qualify to be an author on any of the study publications, an individual should have contributed to the design, conduct, data collection, data analysis, data interpretation, or reporting of the final study. All authors should approve the final manuscript. We will not hire professional writers for the manuscript writing.
References:


Appendix A

Criteria For Defining A Surgical Site Infection (SSI)*

| **Superficial Incisional SSI** | Infection occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision and at least one of the following: 1. Purulent drainage, with or without laboratory confirmation, from the superficial incision. 2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision. 3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culture-negative. 4. Diagnosis of superficial incisional SSI by the surgeon or attending physician. Do not report the following conditions as SSI: 1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration). 2. Infection of an episiotomy or newborn circumcision site. 3. Infected burn wound. 4. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI). |
| **Deep Incisional SSI** | Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision and at least one of the following: 1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site. 2. A deep incision spontaneously dehiscs or is deliberately opened by a surgeon when the patient has at least one of the following signs or |

Note: Specific criteria are used for identifying infected episiotomy and circumcision sites and burn wounds. [433]
symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative.

3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.

4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

Notes:
1. Report infection that involves both superficial and deep incision sites as deep incisional SSI.

2. Report an organ/space SSI that drains through the incision as a deep incisional SSI.

From the CDC guidelines: Centers for Disease Control and Prevention
Appendix D

Definitions

Wound Classification:


BMI Categorization:

Refer to this page on the NIH website.


<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Obesity Class</th>
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<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
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<tr>
<td>Normal</td>
<td>18.5–24.9</td>
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<tr>
<td>Overweight</td>
<td>25.0–29.9</td>
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<tr>
<td>Obesity</td>
<td>&gt;30.0</td>
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### Participant Timeline in the COFACTOR trial

<table>
<thead>
<tr>
<th>Time point</th>
<th>Study Period</th>
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<tbody>
<tr>
<td><strong>Time point</strong></td>
<td><strong>Study Period</strong></td>
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<tr>
<td><strong>Enrolment</strong></td>
<td><strong>Allocation</strong></td>
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<td><strong>Post-allocation</strong></td>
<td><strong>Close-out</strong></td>
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<td>Clinic or hospital admission preoperatively</td>
<td>(Day 0) Day of surgery</td>
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<td><strong>Enrollment</strong></td>
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<td><strong>Eligibility screen</strong></td>
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<td><strong>Informed Consent</strong></td>
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<td><strong>Allocation</strong></td>
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<tr>
<td><strong>Interventions</strong></td>
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<td><strong>Wide suture technique</strong></td>
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<td><strong>Narrow suture technique</strong></td>
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### Assessments

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<tr>
<td>• Gender</td>
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<tr>
<td>• BMI</td>
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<tr>
<td>• DM</td>
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<td>• CAD</td>
<td></td>
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<tr>
<td>• History of inguinal hernia</td>
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<td>• Indication of surgery</td>
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### Outcome Variables

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<td>X</td>
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<tr>
<td>Dehiscence or evisceration</td>
<td>Incisional hernia</td>
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<td>Other Variables</td>
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<td>Reoperation for wound complications</td>
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