3 Protocol TAAD IND127921 180315 Version March 15, 2018

Title: TAAD (Tumescent Anesthesia Antibiotic Delivery) and SubQKath for Reduced Postoperative Opioid Requirements (POR) & Prevention of Surgical Site Infections (SSIs).

WIRB Protocol # **20171606**
Client's Identifying #: **TAAD**
FDA IND# **127921**
ClinicalTrials.gov Registration **# NCT02503904**

0) Title Page & List of Clinical Research Sites

Protocol Title:

Title: TAAD (Tumescent Anesthesia Antibiotic Delivery) and SubQKath for Prevention of Surgical Site Infection in Emergency Colorectal Surgery.

WIRB Protocol # **20171606**
Client's Identifying #: **TAAD**
FDA IND# **127921**
ClinicalTrials.gov Registration **#** NCT02503904

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Financial Disclosure: Jeffrey Klein, MD has several US Patents on devices for tumescent local anesthesia, tumescent anesthesia antibiotic delivery (TAAD) and tumescent platelet inhibition. Dr. Klein's wife, Kathleen Hutton Klein, MD, has an ownership interest in HK Surgical, Inc., which markets devices for tumescent local anesthesia and

Drugs under Consideration: cefazolin, metronidazole, lidocaine, epinephrine.
Other appropriate antibiotics, such as ertapenem, will be included in the TAAD clinicaltrial if approved by the FDA DAIP.

List of Research Sites and Sub-Principal Investigators:

My name is Jeffrey A. Klein MD MPH. I am the principal clinical investigator (PI) for the TAAD RCT. If you have any questions, concerns or suggestions regarding this TAAD PROTOCOL please contact me by email (jeff@kleinmd), or by cellular/mobile telephone (+1 949 283 1070) either by text message or telephone call.

There will be more than one or more research site(s) as listed below. The FDA and the IRB will be provided with a list of all Principal Investigator's (PI) and each PI's curriculum vitae (CV).

Site #	Research Site	Principal Investigator (PI)	Email	Telephone	Site Mailing Address
1					
2					
3					
4					
5					
6					
7					
8					
9					
Etc.					

I) TAAD Protocol: Introduction, Background & Hypotheses

Welcome to the TAAD PROTOCOL.

TAAD (tumescent anesthesia antibiotic delivery) involves a subcutaneous infiltration of TAAD solution consisting of a liter or more of a dilute solution of cefazolin (1gm), metronidazole (500mg), lidocaine (1gm) and epinephrine (1mg) in a liter bag of saline or lactated Ringer's.

TAAD also refers to a FDA (IND#127921) approved multicenter randomized clinical trial (RCT) involving surgical procedures associated with 1) a high incidence of incisional surgical site infections (SSIs), (fecal contaminated emergency colorectal surgery), or 2) a high incidence of severe postoperative incision site pain requiring significant amounts of opioid analgesics (thoracotomy).

When considering the incidence of SSIs in high-risk surgeries, such as fecal-contaminated emergency colorectal surgery, the TAAD trial compares two modes of antibiotic delivery:

- Control: Intravenous Antibiotic Delivery (IVAD)
- Treatment: (TAAD + IVAD)

For the SSI aspect of the TAAD trial, the statistical design consists of a two stage group sequential analysis (with one stopping point). If we assume the risk of an incisional SSI in emergency colorectal surgery is 30% and specify a 50% effect size (a 50% reduction of the incidence of SSI) for the IVAD+TAAD treatment, then the estimated sample size for including both stages of the trial is 216 (108 IVAD controls & 108 IVAD+TAAD treatments).

When considering the incidence of intense postoperative incisional pain, such as thoracotomy, the TAAD trial compares two modes of postoperative anesthesia and analgesia:

- Control: Intravenous Antibiotic Delivery (IVAD) + Nerve Block Anesthesia (NBA)
- Treatment: (TAAD + IVAD + NBA)

where nerve block anesthesia (NBA) may consist of intercostal block, paravertebral block, or thoracic epidural anesthesia. TAAD also provides profound and prolonged (8 to 12 hours) of incision site local anesthesia produced by the tumescent lidocaine anesthesia component of a TAAD solution. For the postoperative pain aspect of the TAAD trial, if we assume that the incidence of suboptimal postoperative thoracotomy pain control is 50% with standard nerve block anesthesia techniques, and if we specify a that TAAD will provide an effect size of 50% defined as a 50% reduction of postoperative pain as measured by visual analog score (VAS) or by patient controlled opioid consumption in the initial 12 hours after incision, then the estimated sample size is approximately 48 subjects, consisting of 24 (IVAD +NBA) and 24 (TAAD +IVAD + NBA).

The Food & Drug Administration (FDA) has approved our Investigational New Drug (IND#127921) application to conduct the TAAD RCT. An IND application was necessary because subcutaneous injection of antibiotics, including cefazolin and metronidazole, is "off-label". In addition, the tumescent formulation of cefazolin (1gm) and metronidazole (500mg/100ml) in a dilute solution of lidocaine (1gm), epinephrine (1mg) in 100ml and sodium bicarbonate (10mEq/10ml) added a 1000ml bag of 0.9% sodium chloride or lactated Ringer's (total volume 1210ml) is also considered "off-label." Western IRB, an institutional review board (IRB), has approved the TAAD trial (WIRB Pr# 20171606) and has designated the SubQKath as a Non-Significant Risk (NSR) for harm to subjects.

"Off-Label" Aspects of Tumescent Drug Delivery
The use of TAAD involves:
1) Subcutaneous antibiotic injection, which is "off-label" for any FDA-approved antibiotic.
2) The very dilute formulation of the antibiotic solution for TAAD, which is "off-label".
3) The recommended safe maximum dosages for tumescent lidocaine (28mg/kg), which is "off-label."

A. Objectives and Purpose of this TAAD Research.

TAAD involves direct subcutaneous infiltration of the TAAD solution. Subcutaneous infiltration of the TAAD solution will be accomplished using specially designed infiltration cannulas such as a Monty infiltration cannulas or SubQKaths. A Full Monty infiltration cannula is a stainless steel blunt-tipped cannula having holes distributed along approximately the distal 85% of the length of the cannula. A SubQKath is a novel over-the-needle subcutaneous catheter, having holes distributed along approximately the distal 85% of the length of the cannula. WIRB has designated the SubQKath as a NSR (Non-Significant Risk) device. FDA 510(k) approval for the SubQKath device is pending.

Surgical Site Infections (SSIs): Despite the use of multiple interventions, SSIs continue to be a significant problem. In emergency colorectal surgery the risk of SSI ranges from 25% in localized contamination to 50% or more in generalized contamination. There is a need for an effective, accessible, inexpensive, simple, safe technique that reduces the risk of SSI in emergency colorectal surgery.

Intravenous antibiotic delivery **(IVAD)** using an over-the-needle intravenous **(IV)** catheter is the current standard mode of antibiotic delivery for SSI prevention. IVAD for SSI prevention is suboptimal because subcutaneous antibiotic concentrations is often sub-therapeutic resulting in an increased risk SSI and of developing antibiotic resistance. For preventing surgical site infections, TAAD overcomes these limitations of IVAD.

The Division of Anti-Infective Products (DAIP) of the FDA has approved an investigational new drug (IND) application (IND#127921) for the present TAAD protocol. The IND application was required because subcutaneous injection of cefazolin and metronidazole, individually and in combination, is off-label. In fact, the subcutaneous delivery of any antibiotic is off-label. TAAD is the first FDA approved IND application for subcutaneous delivery injection of antibiotics.

Post-Operative Incisional Pain: Despite sophisticated regional anesthetic techniques, postoperative pain and opioid requirements continue to be a significant problem. Current techniques for managing post-thoracotomy pain (intercostal blocks, paravertebral blocks, thoracic epidural anesthesia) have significant limitations. There is a need for an effective, inexpensive, simple, safe technique to reduce post-operative incision site pain.

TAAD reperesents the first FDA approved IND application (IND#127921 for subcutaneous infiltration of dilute a tumescent lidocaine solution (with or without antibiotics) at a maximum lidocaine dosage of up to 28mg/kg, which exceeds the current FDA approved maximum recommended dosage of 7mg/kg for infiltration local anesthesia. Because dosages of tumescent lidocaine that exceed 7mg/kg are off-label, there are no CPT billing codes that allow anesthesiologist to be paid for providing tumescent lidocaine anesthesia (TLA). Consequently, most anesthesiologists are unfamiliar with TLA.

Hypotheses:
We hypothesize that TAAD+IVAD is superior to IVAD alone, in terms of reducing the incidence of SSI, venous thromboembolism and systemic inflammatory response syndrome**.**
We hypothesize that TAAD +IVAD + NBA is superior to IVAD +NBA for reducing postoperative incision site pain for any form of nerve block anesthesia (NBA).

These hypotheses are supported by two recently published free open access online journal articles describing the pharmacokinetics of tumescent lidocaine anesthesia (TLA) and the tumescent anesthesia antibiotic delivery (TAAD):

> Klein JA, Jeske DR. Estimated Maximal Safe Dosages of Tumescent Lidocaine. Anesth Analg. 2016;122:1350-9.
>
> Klein JA, Langman LJ. Prevention of Surgical Site Infections and Biofilms: Pharmacokinetics of Subcutaneous Cefazolin and Metronidazole in a Tumescent Lidocaine Solution. Plast Reconstr Surg Glob Open 2017; e1351.

TAAD provides antibiotic concentrations in subcutaneous interstitial fluid that are 10 to 100 times greater than the concentration that can be achieved by IVAD. The lidocaine serum concentration-time profile following tumescent lidocaine anesthesia closely resembles a constant IV infusion of lidocaine. In animal studies, IV lidocaine infusions decrease the incidence and severity of sepsis. TLA lidocaine also inhibits in-vivo platelet function, thus decreasing the risk of venous thromboembolism, while promoting excellent surgical hemostasis. (unpublished data, manuscript in progress).

Tumescent Drug Delivery (TDD)

Tumescent drug delivery (**TDD**)involves subcutaneous infiltration relatively large volumes (0.5L to 2L or more) of a relatively dilute solution of epinephrine (≤1mg) in a liter of either 0.9% physiologic saline or a similar balanced salt solution such as lactated Ringer's solution. From a pharmacokinetic perspective, a dilute tumescent solution functions as a drug delivery vehicle. TDD is a novel mode of drug delivery that has a pharmacokinetic profile distinct from intravenous (IV), intramuscular (IM), oral (PO) or transcutaneous delivery.

When a TDD Solution is used as a vehicle to deliver lidocaine subcutaneously we have TDD solution + Lidocaine = tumescent lidocaine anesthesia **(TLA)**. Further, when an antibiotic is added to a TLA solution, the result is a tumescent anesthetic antibiotic delivery (TAAD) solution.

Subcutaneous tumescent drug delivery provides:
1) High and prolonged (12 to 18 hours or more) localized subcutaneous drug concentrations,
2) Slow steady systemic absorption of drug from subcutaneous tumescent tissue reults in slow steady systemic (serum) drug delivery having a concentration-time profile similar to a slow constant IV infusion
3) At equal doses, the peak serum drug concentration following TDD are substantially **less** than serum concentration following IV delivery thereby averting concentration dependent renal, otic or hepatic toxicity for antibotics having serum-concentration dependent toxicity (e.g. gentamicin). For example, a TAAD solution can be formaulated to contain gentamicin concentration that exceeds the concentration that can be safely achieved by IV delivery, while also is sufficiently dilute enough to avoid causing local tissue toxicity.
4) Some drugs cannot be injected subcutaneously at standard "out-of-the-bottle" concentrations routinely used for IV delivery. For such drugs, the dilution in a TDD solution may avert the potential local tissue toxicity.
5) Drugs that cause pain upon injection, can typically be injected painlessly when added to a tumescent lidocaine solution.
6) Beta-lactam antibiotic concentrations in tumescent tissue following TAAD typically exceed the subcutaneous concentrations achievable by IVAD by a factor of 10 or more. The higher antibiotic tissue concentration achieved by TAAD may overwhelm bacteria that are considered antibiotic-resistant at the lower peak antibiotic concentrations achieved by IVAD.

B. Background: SSI and Subcutaneous Antibiotics:

1) Risk of SSI Colorectal Surgery. In the United States, surgical site infections (SSIs) are a high priority target of hospital quality improvement efforts. [3] In some communities in underdeveloped countries, the incidence of surgical site infections can exceed 30%.

The incidence of SSI depends on several risk factors. Among the common surgical procedures with the highest risk of SSI are colorectal surgeries. The greatest SSI risk factors with respect to patients' health status include obesity, diabetes, advanced age and compromised immunity. The degree of wound contamination is another risk factor, independent of baseline health status. Estimates of SSI rates in elective colorectal surgery range from less than 1% to 15%. But in emergency fecal-contaminated colorectal surgery the incidence of SSI is so high that is often not recorded. However, it is estimated that in emergency colorectal surgeries with focal contamination the incidence of SSI is 20% to 30%. [5] The incidence of incisional SSI in colon perforation with generalized contamination can be as high as 82%. [6] The prevalence of SSI among cancer patients undergoing elective colon and rectal surgery remains high, 23.2 and 27.6% respectively, despite evidence-based preventive procedures. [7] Among obese colectomy patients the risk of SSI is increased by 60%. [8] Low concentrations of antibiotic within peri-incisional tissue is a significant risk factor for SSI in colorectal surgery.[9]

A significant percentage of SSIs becomes apparent after hospital discharge. [10] Retrospective diagnosis of SSI is inaccurate.[11] Reliable research results require good prospective clinical follow-up data collected in a timely manner at least 30 days after surgery.

2) Standard of Care for SSI Antibiotic Prophylaxis. In 1999, The Centers for Disease Control (CDC) published a set of consensus guidelines for SSI antibiotic prophylaxis [**12, 13**]. In 2017, these guidelines were updated [**14**] These guidelines specify rapid bolus IVAD of a sufficient dose of appropriate antibiotic(s) initiated and completed within 60 to 30 minutes of incision, re-administration of antibiotics if the duration of surgery exceeds 4 hours, and discontinuation of antibiotics within 24 hours after incision.

There are two potential problems with the CDC guidelines. Compliance with antibiotic guidelines in clinical practice, especially the timing of IVAD, is often not much better than 60% [**15**, **16**]. Secondly, even with 100% compliance, the incidence of SSI colorectal surgery is still unacceptably high. It is now recognized that IVAD may not always achieve sufficient antibiotic concentration in subcutaneous tissue. Inadequate antibiotic therapy increases the length of stay and cost in complicated SSI [**17**]. Among colectomy patients an SSI increases cost by more than $17,000.

TAAD may provide solutions to these problems. TAAD can be implemented at any time between 0 to 4 hours prior to incision with superior subcutaneous antibiotic concentrations compared to IVAD. Among obese patients, the cumulative antibiotic exposure or area under the curve of the antibiotic concentration-time profile **(AUC)** in subcutaneous interstitial fluid following TAAD is more than 100 times that after IVAD. [**18**]

3) Subcutaneous Bacterial Contamination

Intraoperative contamination of the surgical incision site is the obvious cause of SSI. Among colorectal surgery patients who develop SSI there is an 85% incidence of intraoperative bacterial contamination of the operative field [**19**]. Virtually all bacteria associated with SSI are extracellular pathogens. It is axiomatic that successful antibiotic prophylaxis of SSI requires bactericidal concentrations of antibiotic within the interstitial fluid (ISF) of incised subcutaneous tissue at the time of the incision and bactericidal concentration of the antibiotic that persist over the duration of the surgery.

4) Subcutaneous Antibiotics Are Off-Label.

Subcutaneous delivery of any antibiotic is off-label. The present clinical trial is the first time that the FDA Division of Anti-Infective Products (DAIP) has permitted the subcutaneous injection of antibiotics.

Subcutaneous Cefazolin: The FDA considers the subcutaneous infiltration of cefazolin to be off label. However, the subcutaneous delivery of dilute cefazolin has been described and is recognized as a safe procedure.[**20**] It is common "off-label" practice to inject cefazolin directly into peri-incisional tissues or to sprinkle cefazolin powder directly onto a cut surface of a skin incision at the end of the surgical procedure. These intra-lesional or topical uses of cefazolin are thought to be somewhat ineffective given that the bacterial contamination has already occurred at the time of antibiotic delivery.

The FDA–approved cefazolin package-insert states that cefazolin is indicated for IV or IM delivery. There is no discussion regarding the indication or contraindication for subcutaneous delivery. Apparently, when the cefazolin package insert was written in the early 1970's, subcutaneous delivery was not mentioned. The usual goal of antibiotic delivery is to achieve rapid and complete systemic absorption. IV and IM delivery yield faster and more complete systemic absorption. However, the goal of TAAD in SSI prophylaxis by direct subcutaneous injection is precisely to achieve the slowest systemic absorption with the highest and most prolonged local tissue concentrations of cefazolin.

Subcutaneous Metronidazole: The subcutaneous infiltration of metronidazole is off-label. The FDA approved labeling for metronidazole does not mention subcutaneous injection. Nevertheless, subcutaneous infiltration of metronidazole appears to be safe and effective. **[21, 22**] In state-run hospitals in India, appendicitis is often associated with pre-existing malnutrition and anemia, late presentation, septicemia and gross peritoneal contamination, which lead to a very high wound infection rate. In a study involving 60 patients undergoing exploratory laparotomy for perforation peritonitis with pyoperitoneum, all patients received prophylactic IV antibiotics. The control group, which only received saline irrigation of the incision site, experienced an SSI rate of 66.6% (20/30). The treatment group received subcutaneous infiltration of metronidazole and had an SSI rate of 26.6% (8/30) with ($P < 0.01$). There were no adverse drug reactions attributable to subcutaneous infiltration of metronidazole [**23**].

5) Surgery Impairs Subcutaneous Bioavailability

Antibiotic concentrations in tissue at a surgical incision site following IVAD can be significantly less than the concentration in blood and may be insufficient to prevent the growth of bacteria.

Surgery related hypothermia with peripheral vasoconstriction, tissue trauma, desiccation, edema, inflammation, hemorrhage, hypovolemia, reduced cardiac output, hypotension and capillary thrombosis all decrease perfusion at the incision site and diminish antibiotic transfer from blood onto the incisional surface. Cautery associated char, necrotic tissue, foreign bodies (suture material), incision-surface blood clots, hematomas, and seromas are nidi for infection. The presence of avascular surgical detritus decreases local resistance to bacterial infection and increases the risk of bacterial biofilm formation.

6) Obesity Impairs Subcutaneous Bioavailability

Obesity increases the risk of SSI [24]. Obesity impairs subcutaneous antibiotic bioavailability following IVAD. The area under the curve (AUC) of drug concentration as a function of time is a measure of tissue exposure to a drug. Following IVAD, the ratio $AUC_{tissue}/AUC_{plasma}$ is a measure of antibiotic penetration from blood into tissue. In obese patients this ratio is generally 22% that of normal subjects. In obese patients, the subcutaneous penetration of cefoxitin after IVAD, tested by microdialysis, was less than 10% in 8 of 10 patients. [25]

Ninety minutes after the pre-operative IV delivery of 500 mg metronidazole for intra-abdominal surgery the metronidazole concentration in subcutaneous fat was 36% (4.9 μg/g) of the 13.6 μg/ml in serum as measured by HPLC. [26]

In a study of abdominal wall surgeries 26 patients received metronidazole 500 mg intravenously during induction of anesthesia 2 hours before surgery. Plasma and muscle levels of metronidazole ranged from 5.7 to 15.7 μg/ml, well above the minimum inhibitory concentration for 90 per cent of Bacteroides

fragilis. However, metronidazole concentration in subcutaneous fat (0.6-1.7 μg/ml) did not achieve therapeutic levels. [27]

TAAD is specifically intended for drug delivery into the subcutaneous tissue of obese patients. The thickness of the abdominal midline subcutaneous fat is a more important SSI risk factor than is body mass index (BMI) [28]. TAAD is a simple variation of tumescent local anesthesia (TLA), which in turn was originally developed specifically for patients with thick areas of subcutaneous fat to make liposuction a safer and less painful procedure.

7) Antibiotic Concentration after TAAD

Based on our clinical pharmacokinetic research, at equal antibiotic dosages, TAAD provides antibiotic penetration in subcutaneous tissue, which exceeds that of IVAD by at least 10-fold. In fact, TAAD guarantees that the cefazolin and metronidazole concentration in subcutaneous fat will equal the concentration of the antibiotic within the infiltrated tumescent solution and therefore can be selected to be as high as necessary.

The efficacy of a mode of antibiotic delivery is proportional to the area under the curve (AUC) of the antibiotic concentration-time curve (cumulative antibiotic exposure) within the targeted tissue.

Pharmacokinetic research strongly suggests that TAAD can prevent superficial SSI far more effectively than IVAD. In contrast, in contaminated colorectal surgeries IV antibiotic delivery is more effective than TAAD for antibiotic delivery into deep parenchymal tissues. TAAD cannot be relied upon to produces sufficiently high serum concentrations to prevent septicemia or an intra-peritoneal abscess. Thus TAAD + IVAD ought to be superior to either TAAD or IVAD alone for colorectal surgery.

8) TAAD Benefits

The antibiotic solution for subcutaneous TAAD produces an painless injection, prolonged local vasoconstriction, delayed systemic antibiotic absorption, and prolonged antibiotic exposure within subcutaneous interstitial fluid.

With TAAD the large volume of antibiotic solution both increases local interstitial pressure and acts as a subcutaneous reservoir of antibiotic which together provide a continuous flow of antibiotic solution from the surrounding hyper-hydrated tumescent interstitial space onto the incisional wound surface.

Biofilms can form directly on traumatized desiccated adipose tissue. [34] The elimination of incisional surface tissue desiccation physically prevents bacterial adhesion to wound surface and biofilm formation. The ooze of tumescent antibiotic fluid from the cut surface of the wound is continuous hours after infiltration. This oozing drainage is beneficial in that it delivers a constant flow antibiotic in exceptionally high clinical concentration onto the incision surface thus preventing tissue desiccation and reducing the risk of infection and biofilm formation [35 36 37].

Lidocaine is known to be bactericidal. The TLA component of TAAD may be bactericidal. It is remarkable that the incidence of SSI associated with simple micro-cannula liposuction totally by tumescent local anesthesia, when performed cautiously by well-trained surgeons, is essentially zero. [38 39]

The combination of lidocaine and epinephrine within a TAAD solution produces profound intra-operative local anesthesia and prolonged (approximately 12 hours or more) of post-operative analgesia. TAAD may decrease requirements of general anesthetic agents and post-operative narcotic analgesics and also facilitate earlier post-operative ambulation.

9) TAAD May Reduce Thromboembolism and Blood Viscosity

The leading cause of death associated with liposuction under general anesthesia is pulmonary embolism. [40] In contrast, the incidence of venous thromboembolism following tumescent liposuction totally by tumescent lidocaine anesthesia (TLA) is virtually zero. [41] This remarkable dichotomy might be explained by the antiplatelet activity of lidocaine in a TLA solution. It is known that lidocaine inhibits platelet function. [42 43] There is evidence that lidocaine may reduce the risk of post-operative

thromboembolism. [44 45 46] Our data from an on-going clinical trial among liposuction patients suggests that in-vivo systemic platelet function is significantly reduced after local subcutaneous infiltration of TLA and that the platelet inhibition persists for hours after surgery [47]. With tumescent liposuction totally by local anesthesia, we have observed that there is no difference between preoperative and postoperative platelet count.

TLA contains both lidocaine and epinephrine. Lidocaine inhibits platelet activation. Epinephrine stimulates platelet activation. Lidocaine is a capillary vasodilator. Epinephrine is a capillary vasoconstrictor. Extensive worldwide clinical observation involving millions of tumescent liposuction surgeries accomplished totally by local anesthesia suggests that epinephrine vasoconstriction outweighs lidocaine vasodilation, and lidocaine platelet inhibition outweighs epinephrine platelet activation.

Among colorectal surgery patients, obesity, diabetes, and cancer increase the risk of both SSI and venous thromboembolism (VTE). One study found that among colorectal surgery patients with ulcerative colitis the risk of DVT was 7.4%. [48] In general, colorectal surgery patients have a risk of VTE of 1.6% to 2.4%. [49 50 51] TAAD may reduce the risk of VTE. Another study found that colorectal surgery for cancer had a risk of VTE as high as 16%. [52]

TLA reduces cutaneous and subcutaneous incision site bleeding. The profound localized subcutaneous capillary vasoconstriction induced by the large volume of very dilute epinephrine in a TLA solution reduces both surgical bleeding and the incidence of hematoma. Prior to the use of tumescent local anesthesia, the liposuction aspirate under general anesthesia contained 15 to 30 percent blood and routinely required autologous blood transfusion. [53] In contrast, with tumescent liposuction totally by local anesthesia, this percentage total blood in the aspirate is approximately 1 to 2 percent. [54]

There are no randomized clinical trials which have tested the hypothesis that tumescent lidocaine may significantly reduce the effect of postoperative thromboembolism among high-risk patients after major surgery. In the present multicenter randomized clinical trial, the occurrence of post-operative deep vein thrombosis or pulmonary embolism will be an important secondary outcome variable.

10) TAAD Infiltration: Timing & Technique. See also section **iv F.** Method and Devices for TAAD Infiltration.

Timing for TAAD: Although TAAD can be infiltrated in the OR immediately prior to surgery, the optimal timing for doing TAAD infiltration may be 1 to 4 hours prior to surgery. A span of 1 hour or more between TAAD infiltration and surgical incision allows time for detumescence to occur.

Detumescence, an important aspect of TAAD, is the process by which the tumescent tissue gradually becomes less swollen over an hour or more following completion of tumescent infiltration. After detumescence, both the gross appearance of the incised fat and the ease of surgical manipulation become more normal. Infiltrating a sub-optimal volume of tumescent solution can reduce the time required for detumescence. However, any volume reduction or elimination of the lidocaine and epinephrine components in a TAAD solution is likely to adversely affect the duration and efficacy of the antibacterial, antiplatelet and postoperative analgesic effects of TAAD. [55 56]

Location for Doing TAAD: Infiltration of TAAD solution can be accomplished either 1) in the patient's hospital room, 2) in the pre-operative area prior to entering the operating room (OR) or 3) in the OR. The advantage of completing TAAD before entering the OR, is that the infiltration process can be performed by a nurse rather than a physician. When TAAD is done in the OR, the infiltration process may take-up valuable OR time, add to the work of a busy OR staff or delay the incision.

The timing of TAAD is not as critical as is the timing of IV antibiotic delivery. Current SSI prophylaxis guidelines mandate a 30minute window for IVAD (within 30 to 60 minutes before incision) in order to optimize subcutaneous antibiotic concentration at the time of incision. If delivered too early peri-incisional interstitial fluid **(ISF)** concentrations of antibiotic will have declined concomitantly with the exponential decrease of serum concentrations after bolus IVAD. If IVAD is done too late then there will be insufficient time for antibiotic to be transferred into the incision site ISF before incisional trauma and bacterial contamination occur. [57 58 59 60]

Compliance with recommended dosing schedules for prophylactic antibiotics in colorectal surgery is less than optimal. Because of competing workflow demands in a busy operating room, this 30minute target can be missed 40% of the time. [61]

TAAD has the potential to relax this time-constraint by delivering a long-lasting high concentration of antibiotic into subcutaneous tissue hours before the patient enters the operating room. High subcutaneous interstitial fluid antibiotic concentrations persist for at least 12 hours or more after infiltration. When TAAD is followed by IVAD, the resulting subcutaneous and systemic antibiotic concentrations are more likely to be sufficient, even if IVAD is only done within minutes before incision.

TAAD is preferably done before entering the operating room (OR). TAAD infiltration can be done in either a patient's hospital room or a pre-op preparation area under minimal sedation. A physician, a registered nurse or a physician assistant can do the infiltration of TAAD solution using tumescent infiltration cannulas (HK SubQKath), peristaltic infiltration pump (HK KTP) and infiltration tubing (HK KIP-II infiltration tubing).

Because the patient is awake with minimal sedation, minimizing patient discomfort during infiltration is a priority. Painless tumescent infiltration is not difficult to achieve, especially in obese patients, but does require a careful attention to detail. Subcutaneous insertion of a SubQKath requires a careful technique with attention maintaining the SubQKath within subcutaneous tissue and avoiding penetration through deep fascia.

II) Subject Recruitment, Enrollment, Consent/Assent

vi. Subject Identification, Recruitment and Consent/Assent

A. Method of Subject Identification and Recruitment: The primary method of recruitment will involve a discussion between the prospective research subject and the surgeon or the surgeon's staff. Patients who are already scheduled to have one of the targeted surgical procedures will be offered the opportunity to participate in this study. There will be no public advertising or public recruiting.

B. Process of Consent: Each participating surgeon or the surgeon's designated staff member, such as another knowledgeable and experienced physician, physician's assistant or registered nurse, will discuss and obtain informed consent from every patient or the patient's designated guardian in case of emergency surgery.

C. Subject Capacity to Give Informed Consent: All prospective adult subjects must be fully capable of comprehending and giving their own informed consent or, in case of emergency surgery, the patient's designated guardian must be fully capable of comprehending and giving informed consent.

D. Subject/Representative Comprehension: All prospective adult subjects or a designated guardian must be fully capable of comprehending and giving their own informed consent.

E. Debriefing Procedures: This is not a psychological study. The only formal debriefing will consist of post-operative follow-up telephone call(s) to or from the patient and/or a free return follow-up office visit by the patient to meet with the surgeon or one of the surgeon's research assistants. All patients will have the opportunity to meet personally with the surgeon before or after the surgery and as often as necessary to discuss any questions and address any concerns that a patient might have regarding the surgery or the research project.

F. Consent Forms: To document informed consent, all subjects will sign at least three consent forms: IRB Research Consent Form (individual research sites will have their own IRB-approved consent forms), the HIPAA Consent Form in addition to the research site's standard surgical consent form.

G. Documentation of Consent: Patient consent forms will be placed in the patient's research chart. The chart will be kept in a locked filing cabinet.

H. Cost to the Study Subject: Study subjects will pay for the cost of transportation to visit the surgeon for follow-up visits. If research funding is obtained, then subjects may be offered payment for their transportation expenses for follow-up visits. There is no extra charge or extra expense to the patients/subjects for participating in this research project. There is no charge to the patient for routine follow-up visits which are scheduled as part of this research project.

I. Payment for Participation: Volunteer subjects will not be paid for participation in this research project.

Research sites will not be paid by the sponsor of this research for participation in this TAAD research. Individual researchers will not be paid by the by the sponsor of this research for participation in this TAAD research.

III) Important Clinical Guidelines

Please note the following import Guidance for the TAAD Clinical Trial Protocol

Guidelines for Preparation of TAAD Solutions

1. Use USP grade diluents (0.9% physiologic normal saline and sodium bicarbonate or lactated Ringer's solution and sodium bicarbonate) to prepare the TADD solution.

2. Use freshly prepared TADD solution but stored not longer than 4 hours.

3. Inspect the TADD solution at the time of preparation and immediately before use for visible precipitation or the presence of particulates in the TAAD solution. Discard if the solution if it is hazy or discolored.

4. The TAAD solution is considered "off-label" and is only for investigational use as part of this RCT which has IND approval by the FDA.

5. The following label(s) must be applied to each bag of TAAD solution immediately at the time of preparation:

"Caution: This TAAD solution contains 1 gram of lidocaine. Not for IV infusion.
"Caution: This TAAD solution is only to be used for subcutaneous infiltration" and
"Caution: New Drug – Limited by Federal (United States) law to investigational Use."
for example:

Caution !!

Not for IV infusion

TAAD Solution

For Subcutaneous Injection Only

Contains 1 gram of Lidocaine

Caution: New Drug

Limited by United States Law to Investigational Use

TAAD Clinical Guidelines

1. A patient may receive a maximum of two TAAD bags of TAAD solution. Each bag of TAAD solution contains cefazolin (1gm), metronidazole (500 mg/100ml), lidocaine and 1 mg epinephrine and 10 mEq sodium chloride in either normal saline or lactated Ringer's solution, for a total volume of approximately 1210ml. See Table 1
2. Maximum mg/kg dosage of tumescent lidocaine with TAAD is 28 mg/kg. Each bag of TAAD solution contains 1000mg of lidocaine. For a patient weighing 70kg or more, the permitted total volume of TAAD solution is 2 liters. If the patient weighs less than 70kg, the total volume of TAAD solution must be proportionately reduced. Thus, for a 50kg patient the maximum ml volume of TAAD solution should not exceed approximately (50/70) x 2 liters = 1.5 Liters.
3. Cefazolin & metronidazole are the only two antimicrobial drugs permitted to by the FDA IND approval to be in the TAAD solution.
4. Patients are excluded from participation in TAAD RCT if there is clinically significant renal impairment (elevated serum creatinine), hepatic impairment (clinically significant elevation of liver function tests) or cardiac impairment (moderate to severe congestive heart failure). Patients with normal or borderline elevated serum creatinine may participate in the TAAD clinical trial. Patients with definite and clinically significantly elevated serum creatinine concentrations (not simply associated with dehydration) and confirmed by repeated testing are to be excluded from the TAAD clinical trial.

IV) Risk & Benefit Discussion

W. Risk/Benefit Assessment
1. Risk Category: The risk category for this research project is **minimal**.

2. Safety of TAAD: The safety of each drug component within the Tumescent Antibiotic Delivery (TAAD) solution is well established (See References). These drugs include dilute cefazolin, dilute metronidazole, dilute lidocaine, dilute epinephrine, dilute sodium bicarbonate, and physiologic 0.9% saline. In the previous WIRB-approved research all of these TAAD drugs have been used without any evidence of adverse effects. The following peer-reviewed publications document the results of this research:

Klein JA, Jeske DR. Estimated Maximal Safe Dosages of Tumescent Lidocaine. Anesth Analg. 2016;122:1350-9.

Klein JA, Langman LJ. Pharmacokinetics of subcutaneous cefazolin and metronidazole in a tumescent lidocaine solution for prevention of surgical site infections and biofilms. Plast Reconstr Surg Glob Open 2017; e1351.

There were no adverse events related to the drugs or procedures in these clinical trials.

3. Safety of lidocaine and tumescent local anesthesia: The safety of Tumescent Lidocaine Anesthesia (TLA) is well established. TLA has been used on millions of patients and is recognized as the worldwide standard of care for safe liposuction totally by local anesthesia. Each of the pharmacologic agents is a generic drug with a well-established safety profile. These include Lidocaine, Epinephrine, Sodium Bicarbonate, and physiologic 0.9% saline or lactated Ringer's solution. This publication estimated that 28mg/kg without liposuction (with or without general anesthesia), has a risk of mild lidocaine toxicity (serum lidocaine concentration $\geq 6\ \mu$ g/ml) of 1 per 5,000,000.
4. Safety of Tumescent Infiltration Technique and Devices: The techniques for tumescent infiltration are well established and is currently used by thousands of surgeons worldwide. All devices to be used in the present research will have FDA 510(k) or IDE clearance/approval.
5. Safety of Epinephrine: The dosages of tumescent epinephrine that will be used in the present clinical trial have been well established as safe and effective. The results of the research reported in the following two publications showed no evidence of epinephrine related tachycardia.

Klein JA, Jeske DR. Estimated Maximal Safe Dosages of Tumescent Lidocaine. Anesth Analg. 2016;122:1350-9.

Klein JA, Langman LJ. Pharmacokinetics of subcutaneous cefazolin and metronidazole in a tumescent lidocaine solution for prevention of surgical site infections and biofilms. Plast Reconstr Surg Glob Open 2017; e1351.

6. Safety of Cefazolin and Metronidazole: The safety of subcutaneous delivery of dilute cefazolin and dilute metronidazole is well established in the literature, both for preventing SSI and for palliative treatment of terminally ill patients (see references). In the present clinical trial, the mg/kg dosages of cefazolin and metronidazole will conform to community standards of care.

X. Potential Risk of TAAD and TLA:
Infiltration Cannula. There are two types of infiltration cannulas that have been designed for subcutaneous tumescent infiltration: 1) SubQKath is a disposable over-the-needle plastic cannula specifically designed for TAAD and 2) Monty infiltration cannulas are stainless steel blunt tipped cannulas (having tiny holes distributed distally along 50% to 90% of the cannula length) that were originally designed for infiltration of tumescent lidocaine anesthesia for large surgeries totally by local anesthesia.

"Painless" infiltration of TAAD in a fully awake patient requires the brief use of a sharp needle (for example, a spinal needle) inserted into subcutaneous fat for initiating the tumescent infiltration. There is a risk of puncture of deep anatomic structures associated with the use of spinal needles. The risk of injury from this needle is minimized by a careful infiltration technique: The needle is held in the clinician's dominant hand and advanced parallel (tangential) to the sub-dermal plane, while the contralateral hand gently grasps and elevates the skin as the needle is carefully advanced with the needle tip continuously located between the finger and thumb of the contralateral hand. After this brief initial phase of tumescent infiltration, a larger gauge (typically 18gauge or 16gauge) blunt-tipped Monty infiltration cannula is inserted into the subcutaneous tissue and used for infiltrating the remaining 90 percent or more of the TAAD solution.

Potential Risks of SubQKath include
1) Penetration or puncture of tissue deep to subcutaneous tissue. This risk is minimized by careful clinical insertion technique, which includes grasping the subcutaneous tissue with the non-dominant hand and maintining the tip of the SubQKath well above fascia and continuously between the fingers and thumb of the non-dominant hand as the SubQKath hub is held in the dominant hand while advancing the SubQKath through the subcutaneous tissue.
2) Laceration of the SubQKath plastic catheter by the sharp stainless steel stylet. This risk is avoided by never re-inserting the stylet into the catheter once the stylet has been withdrawn.

Y. Protection against Risk
1) Criteria for terminating the study include:
a) The surgeon determines that it is unsafe, unethical or unreasonable that a patient continue to participate in the research project.
b) The patient does not tolerate infiltration of tumescent local anesthesia because of anxiety or discomfort. (As an alternative, the patient can be given the option for the tumescent local anesthesia to be infiltrated by the surgeon after induction of general anesthesia and before the incision).
2) Monitoring for toxic or adverse drug events: Patients will be observed and questioned with respect to any signs or symptoms of adverse reactions to the drug used for TAAD including rash, dyspnea, heart palpations, irregular heart rate, chest pain, headaches, focal weakness, confusion, gastrointestinal irritation, hematemesis, black tarry stools. The risk of an allergic adverse event with TAAD should be no different than that associated with IV antibiotic delivery.
Z. Potential Benefit to the Subject:
There is no guarantee that volunteer subjects will receive any medical benefits from being in this study. The patient may benefit by having a decreased risk for a surgical site infection or a venous thromboembolism. All patients who participate in this research project will routinely receive the "standard of care" methods for preventing a surgical site infection and for preventing a post-operative blood clot in a leg or lung. Approximately 50 percent of the volunteer subjects will receive both the "standard of care" intravenous (IVAD) preventive treatments for SSI and an additional treatment in the form of an antibiotic solution injected directly into the subcutaneous fatty tissue surrounding the site of the incision (TAAD). If TAAD proves to be optimal for preventing SSI among patients having GI surgery, trauma surgery or burn surgery then it is likely TAAD will also be beneficial for future use in other patients having similar or other types of surgeries.
ZZ. Alternatives to Participation:
Persons do not have to participate in this study to have an appropriate surgical procedure. Any prospective volunteer subject may choose to have the routine "standard of care" methods for preventing a surgical site infection and for preventing a post-operative blood clot in a leg or lung without participating in this study.

V) Study design

Number of Subjects:
Assuming a 14% incidence of SSI, and considering a 50% reduction in the risk of SSI with TAAD as a clinically significant improvement (effect size = 50%) our sample size analysis estimates that **approximately 330 to 660** subjects will be required to achieve a statistical power of 0.8 (We used a **group sequential statistical analysis** with one intermediate stopping point at 330 patients. See statistical analysis for sample size estimates and power analysis).

This multicenter randomized clinical trial (RCT) protocol is designed to
1) compare IV antibiotic delivery (**IVAD**) to IVAD plus TAAD, (**IVAD+TAAD**),
2) prospectively validate the safety of tumescent lidocaine at dosages up to 28mg/kg,
3) prospectively validate the safety of the SubQKath for tumescent anesthetic antibiotic delivery (TAAD),
4) prospectively validate the use of KTP peristaltic infiltration pump (HK Surgical, Inc.) for TAAD.

Type of Clinical Trial: This research is an open label controlled randomized clinical trial **(RCT)** comparing two modes of antibiotic delivery. It is not a trial comparing antibiotics. This protocol describes an open label randomized clinical trial **(RCT)** with prospective multicenter meta-analytic statistical design using sequential data analysis with one stopping point. Individual research sites will choose the targeted category of research subjects based on each site's population of surgical patients and the clinical interests of the participating surgeons. The total number of research sites and investigators is not predetermined.

Ideal Patients. The ideal patients for participation as subjects in the TAAD clinical trial are those at high risk for SSI. From a statistical perspective, studying SSI among subjects with the highest risk of SSI minimizes sample sizes requirements for a given effect size and optimizes statistical power. Thus, target populations for the present clinical trial are patients who have a high risk of SSI. These may include patients exposed to high-risk surgical procedures (open abdominal surgeries, trauma surgeries, burn surgeries, sternotomy, repair of recurrent ventral hernia) or patients who are obese, have diabetes, are immune-compromised or are otherwise at increased risk of SSI.

Types of Surgical Procedures: Some research sites may be sophisticated high-tech medical centers caring for the most difficult colorectal surgical patients at exceptionally high risk for SSI. Some research sites may serve medically impoverished populations with limited surgical resources and very high rates of SSI due to malnutrion or diabetes. Other research sites may be focused on the care of patients in burn centers, trauma patients with contaminated wounds, military combat casualties with grossly contaminated wounds, patients with infected median sternotomy wounds undergoing muscle flap repair, or patients undergoing repair of ventral incisional hernia.

Within any given research site research subjects (patients) having similar surgical procedures will be randomly assigned prospectively to either **IVAD** (control) or **TAAD+IVAD** (treatment).
Any research site can provide different types categories surgical procedures. Thus, the type of surgical procedure may vary from subject to subject provided that all subjects receiving a given surgical procedure are grouped together and then randomly assigned to receive either IVAD or IVAD+TAAD.

Scientific Generalizability

In order to maximize the generalizability of the results of this research, the protocol is designed to accommodate a wide variety of pathology, surgical techniques, surgeon training/experience, quality of surgical facilities, diverse local health, local nutrition and local economic conditions. The protocol specifically allows for the use of locally available antibiotic products. Individual research sites will use their usual and customary sources of cefazolin, metronidazole, lidocaine, epinephrine, sodium bicarbonate and physiologic salt solutions. This protocol explicitly allows the use of any generic version of the antibiotic, irrespective of the manufacturer.

Tumescent Infiltration Devices

Disposable, single use tumescent infiltration tubing and tumescent infiltration catheters will be provided by the sponsor for TAAD for use in patients participating in this TAAD research.

Each research site will be provided with one KTP tumescent peristaltic infiltration pump. Research sites will be responsible for the careful use and maintainence of its KTP pump. The research site is responsible for lost or misplaced KTP pump(s). After a research site has enrolled and reported the research data for at least 10 TAAD research subjects, the research site will be given its first KTP infiltration pump. If a research site does not enroll 10 subjects during the course of the research, then the KTP pump will be returned to the sponsor. Research sites can purchase additional KTP pumps (at cost) for continued research purposes. The purchase price for additional KTP pumps will be the same as the cost to the sponsor for the KTP pumps.

Choices of Antibiotics

Antibiotics for TAAD. Only cefazolin and metronidazole can be used for TAAD. Only cefazolin and metronidazole have FDA approval (IND#127921) for subcutaneous infiltration of TAAD solution for the TAAD research. The FDA considers the subcutaneous injections of virtually all antibiotics to be off label.

Antibiotics for IVAD. The choice of antibiotic to be used for IV antibiotic delivery (IVAD) for patients receiving either IVAD alone or concomitant IVAD+TAAD is up to the discretion of the surgeon. There is no requirement that cefazolin or metronidazole be used for the IV antibiotic delivery. The antibiotic for IV antibiotic delivery can be the surgeon's standard "antibiotic of choice." However the antibiotics TAAD component must only be metronidazole and cefazolin.

Antibiotic Consistency. Within any individual research site, it is preferred that the antibiotic brands and formulations will be standardized and invariant, subject to continued availability of the antibiotic.

Drug Expenses. Each research site is responsible for providing the necessary cefazolin, metronidazole, lidocaine with epinephrine, sodium bicarbonate and 0.9% physiologic saline or lactated Ringer's solution. In some medically indigent communities, for every enrolled research subject (patient) the sponsor will reimburse individual research sites for the cost of these drugs.

Statisitical Issues

Patient Stratification and Matching

For every patient the ASA classification, wound contamination classification, degree of trauma or degree of burn will be recorded. This multicenter clinical trial is specifically designed to be inclusive of

different surgical procedures. This RCT design will accommodate a large range of research sites and surgical procedures and improve the generalizability of results.

The following classification of patient characteristics and surgical procedures will be recorded

1. Immunocompromised and cancer patients
2. Obese patients,
3. Diabetics,
4. Emergency operations, as designated by the surgeon, will be included only with the appropriate approval of the institutional IRB at the individual research site. Emergency cases will be classified together with other emergency patients.

In order to facilitate multivariate analysis and minimize variance, the status of each patient with respect to immunosuppression, cancer, obesity, diabetes and emergency surgery, will be recorded. Patients will be matched with respect to age, sex, weight, surgical procedure, presence of diabetes, presence of obesity, and presence of immunospression.

Primary and Secondary End Points

The primary end-point presence of surgical site infection (SSI). This is a binary (Yes/No) variable.

This protocol is also intended to prospectively collect data to evaluate the safety and efficacy of the devices (HK SubQKath, HK tumescent infiltration tubing and HK peristaltic tumescent infiltration pumps) used for subcutaneous tumescent infiltration of TAAD solutions.

The protocol compares TAAD + IVAD with IVAD alone with respect to:
1) the the occurance of SSI,
2) the occurance of post-operative venous thromboembolism (VTE) and
3) the occurance of sepsis (pathogen-related or damage-related).
The protocol also records device-related incidence of adverse events. The devices used for TAAD include a new single use subcutaneous infiltration cannula (HK SubQKath) or multiple use (autoclavable) stainless steel infiltration cannulas, tumescent drug delivery, tumescent peristaltic pumps and tumescent infiltration tubing.

Definition of TAAD: Tumescent anesthesia antibiotic delivery **(TAAD)** is defined as the subcutaneous infiltration of a dilute solution of antibiotic(s) in a solution of tumescent lidocaine anesthesia **(TLA).** In this research the TAAD antibiotics consists exclusively of cefazolin 1gm and metronidazole 500mg (in 100ml).

Definition of TLA: Tumescent lidocaine anestheisia (**TLA**) consists of a dilute solution of lidocaine (1gm per liter bag), epinephrine (≤1mg per liter bag) and sodium bicarbonate (10mEq per liter bag) in one liter of 0.9% physiologic saline or lactated Ringer's solution. The maximal dosage of TLA lidocaine is 28mg/kg without liposuction.

The Principal aim of this research is to compare IV antibiotic delivery (IVAD) to (TAAD+IVAD) with respect to the prevention of SSI.
The secondary aims of this study are to compare TAAD+IVAD vs IVAD with respect to the
1) prevention of post-operative venous thromboembolism **(VTE)**, and
2) prevention of post-operative sepsis (pathogen related or trauma related).

Hypotheses: We hypothesize that TAAD together with intravenous antibiotic delivery **(IVAD)** will significantly reduce the incidence of surgical site infections (**SSI**).

Primary Outcome Variable is the detection of a surgical site infection (detected within 30 days of surgery): The infection may be superficial, deep incisional, organ space.

Secondary Outcome Variables

1. Diagnosis of Venous Thromboembolism (VTE) either deep vein thrombosis (DVT) or Pulmonary embolism (PE) within 30 days of surgery (Binary Data)
2. Diagnosis of Sepsis, including systemic inflammatory response syndrome (SIRS)
3. Safety of TAAD and TLA (incidence of adverse events associated with subcutaneous antibiotics or local anesthesia
4. Device safety and efficacy: peristaltic tumescent infiltration pump and subcutaneous tumescent infiltration catheter (SubQKath).

Other Outcome Variables

1. Post-Op ICU admission (or equivalent unit) and number of hours in ICU
2. Length of Stay (LOS) in hospital after surgery (hours)
3. Post-Op Narcotic Requirements (total mg and mg/kg)
4. Unexpected re-admission to hospital (for any reason) ≤ 30 days of surgery (Binary Data)
5. General Anesthesia Requirements (Quantitative Measure)
6. Diagnosis of C. Difficile colitis

Timing of Antibiotic Delivery

•**IVAD timing**: For IVAD alone (without TAAD), the goal is for the IVAD infusion to be completed within 30 to 60 minutes prior to surgical skin incision. The actual time from start to completion of IVAD will be recorded.

•**TAAD timing** and technique: TAAD infiltration is to be completed less than 4 hours prior to skin incision. For subjects receiving IVAD + TAAD, the IVAD will be initiated and completed any time between 60 minutes to 5 minutes before the initial incision. The actual time of the completion of the TAAD and the completion of IVAD will be recorded.

Hospital Site for Antibiotic Delivery

The surgeon, anesthesiologist and patient will decide on the appropriate timing and location for TAAD infiltration. The TAAD infiltration procedure can be accomplished any of the following hospital settings:
1) in the patient's hospital room with the patient alert and awake with no sedation or with mild sedation,
2) in the pre-op area before the patient enters the operating room with the patient awake with no sedation, with mild sedation or monitored with IV or IM sedation,
3) in the operating room with the patient is under general anesthesia or heavy IV sedation.

Criteria for Diagnosis of SSI, VTE & Sepsis

Criteria for SSI will be defined by the criteria of the Centers for Disease Control updated and published August 2011. [64] See www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf.

"**Significant SSI**" is defined as a SSI that requires the use of additional health care resources. Only significant SSI will be considered in the final statistical analysis. This will avoid confounding effect of including "false-positive" results associated with trivial or normal incision-site inflammation or tumescent fluid drainage from an incision site. We recognize that the CDC definition of SSI includes elements that cannot easily be standardized such as a clinical diagnosis of SSI by a clinician, or the clinical decision to submit wound swabs for bacterial culture.

Diagnosis of VTE. Criteria and methods for diagnosis of venous thromboembolism **(VTE)** to be determined and standardized by each research site.
Diagnosis of Sepsis. Criteria and methods for diagnosis of sepsis to be determined and standardized by each research site.

Questionnaires & Methods to Reduce Bias in Outcome Determination

All subjects participate in **four (4)** separate questionnaires. In addition, patients who receive TAAD will be given an additional brief questionnaire inquiring about the TAAD experience.

1) Pre-Op Questionnaire: The Pre-Op Questionnaire will help determine the eligibility of the prospective research subject to participate in the TAAD RCT

1+) TAAD Questionnaire: Immediately after completion of a TAAD infiltration, patients will be given a very brief post-TAAD infiltration questionnaire asking about the discomfort, pain or anxiety associated with TAAD.

Post-Op Questionnaires: Post-operative questionnaires concerned with determining the occurrence of SSI, VTE, Sepsis will not contain questions that would allow the interviewer to determine infer or guess which mode of antibiotic delivery was assigned to the subject. The person who conducts the interview will be instructed not to discuss the mode of antibiotic delivery.

2) Day-1 (24-hour) Post-Op Questionnaire is to be completed within 18 to 36 hours after surgery. This questionnaire will include questions regarding possible acute local (surgical site) tissue toxicity and acute systemic toxicity.

3) Day-14 or Discharge Questionnaire is to be completed on the 14th day of hospitalization or at the time of hospital discharge, whichever occurs first. This questionnaire will inquire about possible SSI, VTE or Sepsis during hospitalization. This questionnaire will also inquire about side effects of TAAD and IVAD. The number of post-op days at the time of this questionnaire will be recorded.

4) Day-30 Post-Op Questionnaire or Post-Discharge Survey **(PDS)** to be completed within 30 to 45 days after surgery. This questionnaire will be completed on day 30 if the patient remains hospitalized (original hospitalization) or if the patient in-hospital on day 30 because of a re-admisson to hospital.

5) Day-365 Post-Op Questionnaire For Implant Patients. If the surgery involves an implant, then the patient will be contacted one year after surgery and asked to answer the Day-365 Post-Op Questionnaire.

Drug Side-Effects Questions: The questionnaires on Day-1 and Day-14 will ask about possible side effects of tumescent antibiotic delivery (TAAD) or IV antibiotic delivery (IVAD). The questionnairs will inquire about possible acute incision-site tissue toxicity and acute systemic toxicity and drug-reaction including cutaneous drug eruption. The person assigned to administer the day-1 and day-14 questionnaires will be instructed to not discuss or ask about TAAD.

V. Methods of post-discharge surveillance for SSI or VTE

Fundamental to the prospective design of this clinical trial is a feasible, valid, reliable and standardized means of defining and detecting SSI and/or VTE during hospitalization and after discharge. Patients who have an SSI or VTE diagnosed after discharge or admitted to a different hospital within 30days of discharge from the research site will be identified by one of the following Post-Discharge Survey **(PDS)** techniques:

1. Follow-up clinical interview and questionnaire. The interview and questionnaire will be conducted by a designated health care professional 30 to 45 days after surgery.
Because of logistical and economic constraints additional PDS methods may include:
2. Post-discharge questionnaire for patient (telephone, text message, online website survey, mail or email)
3. Cards given to patients to facilitate notification of health care personnel of a SSI or VTE by mail, email or telephone call
4. Medical record chart review with the intent to identify

a. Readmissions
b. Additional surgical procedures
c. Positive cultures obtained during hospitalization or after discharge
d. Review of operating logs to search for evidence of a surgical revision
e. Review of Radiology/Ultrasound diagnostic tests

5. Data Collection Guidelines and data collection forms will be specified in the researchers' handbook.

6. Data Monitoring Guidelines will be specified in the researchers' handbook.

7. Monitoring for Adverse Events: in addition to search for evidence of SSI and VTE, clinical observation will document any evidence of rash, subcutaneous tissue inflammation or toxicity, dyspnea, heart palpations, irregular heart rate, chest pain, headaches, focal weakness, confusion, gastrointestinal irritation, diarrhea, hematemesis, black tarry stools and other adverse events.

Location and Description of Surgical Facilities

All surgeries will be performed in surgical facilities or hospitals that have been accredited by the local or state government. Specific research sites and surgical facilities remain to be determined.

Duration of Subjects' Research Participation

Pre-Op: For research subjects in this clinical trial there should be minimal extra time-commitment before the day of surgery. Pre-operative history, physical examination, diagnostic evaluation and clearance procedures prior to the surgery should not require the patient to spend any extra time prior to the surgery. Some cases might require pre-operative clearance by a medical specialist such as a cardiologist, nephrologist or hematologist

Post-Op: After the surgery, the research staff will contact the patient for one or two brief postoperative follow-up conversations and questionnaires. Thirty to 45 days after surgery, all subjects will be required to participate in a follow-up interview and questionnaire, either in-person or by telephone. If a subject has experienced a possible surgical site infection or a possible post-operative blood clots in the legs or lungs or sepsis then a follow-up examination may be required.

List of Research Procedures to be used to accomplish the specific aims of the project:

1) Subcutaneous tumescent anesthesia antibiotic delivery (TAAD)
2) Clinical questionnaires

Data Storage and Confidentiality:

All data and clinical records will be stored in a secured area at the respective research site. In addition, the data from all research sites will be collected by the Data Monitoring Committee and maintained in a secure fashion. Confidentiality will conform to HIPAA requirements.

Transition from Research Participation:

Patient research participation will end at the conclusion of the 30 to 45 day post-operative follow-up period, except for possible routine clarification of questionnaire answers. Subsequent routine non-experimental clinical care for each patient will continue with the patient's surgeon and primary care physicians.

VI) Eligibility Criteria (inclusion/exclusion)

Criteria for Subject Selection

A. Gender of Subjects

This study will involve both males and females.

B. Age of Subjects:

Participating volunteer patients must be at least 18 years old.
Pediatric patients will not be enrolled.

C. Racial and Ethnic Origin

There is no restriction on participation with respect to racial or ethnic origin.

D. Inclusion Criteria (Eligibility criteria for participation as a research subject include:

1. Subjects greater than 18 years of age scheduled for surgical procedures considered to have a high risk for a surgical site infection (SSI) such as 1) secondary repair of a ventral hernia, 2) open bariatric surgery, 3) open abdominal colorectal surgery, 4) trauma surgery, 5) burn surgery or 6) sternotomy dihisance.

2. Patients ought to have one of the following risk factors for surgical site infection: emergency surgery, obesity, diabetes mellitus, cancer surgery, be immune-compromised, or otherwise be at an increased risk for SSI, or be in a medically indigent environment where surgical aseptic technique is suboptimal

3. Only adults will participate as research subjects, unless there is specific FDA approval to enroll persons less than 18 years of age.

4. Patients in ASA (American Society of Anesthesiology) class (I or II or III) will be included.

5. For each patient, the wound classification, ASA classification, trauma and burn classification will be carefully recorded.

6. Abdominal wound classifications: Clean-Contaminated, Contaminated, or Dirty are eligible to participate. Patient having open abdominal surgery will be matched with respect to wound cleanliness classification.

7. Patients must be appropriately screened for the proposed surgery.

E. Exclusion Criteria: Potential subjects will be excluded because of any of the following:

1. Procedures involving only simple ostomy closures

2. Known allergy to cefazolin or metronidazole or an antibiotic preferred and routinely used by the surgeon

3. Persons less than 18 years old, unless there is specific FDA approval to include persons < 18 years.

4. Emergency operation as designated by the surgeon will be included only with the appropriate approval by the institutional IRB at an individual research site

5. Pregnant or breast-feeding women are excluded.

6. A known bleeding/hemorrhagic/thrombotic disorder is exclusionary unless there is a written clearance chart-note or clearance letter from a primary care physician or hematologist

7. Significant psychiatric problems which might impair ability to give truly informed consent or which may impair follow-up communication with the surgeon and staff

8. Clinically significant cardiac arrhythmias are exclusionary unless there is a written clearance chart-note or clearance letter from a cardiologist

9. Heart/liver/kidney disease, neuropsychiatric disease classifying patient as ≥ ASA IV or V

10. Major concomitant infections such as pneumonia or sepsis

11. In non-emergency surgery, pre-existing active bacterial skin infection at the time of the surgical incision; however, pre-existing bacterial infections are not exclusionary in burn or trauma patients.
12. Foreign material in the incision that cannot be removed
13. Recent systemic antimicrobial therapy
14. Clinically significant renal impairment or a creatinine clearance < 30 mL/min.
15. Severe congestive heart failure (CHF) requiring pharmacologic therapy or an ejection fraction ≤ 40% or orthopnea and dyspnea upon exertion.
16. Severe hepatic insufficiency associated with a either a clinical diagnosis of hepatic insufficiency or a laboratory diagnosis based on chronically elevated ALT, AST, PT, PTT and hypoalbuminemia.

F. Vulnerable Subjects that are Excluded

1. Pregnant women are excluded
2. Nursing home residents, or other institutionalized persons who are not fully alert, not cognizant or and not able to give informed consent are not eligible to participate as a research subject, are excluded
3. Children < 18 years of age are excluded, unless there is explicit FDA approval of participation of pediatric patients.

VII) Drugs: Formulation, Dosages, Modes of Administration

A. MAXIMUM VOLUME OF TAAD SOLUTION

The maximum volume of TAAD solution is two bags, where each bag contains 1210ml of TAAD solution. Most patients will receive 1 bag (1210ml) of TAAD solution. Obese patients may require up to two (2) bags of TAAD solution. Very thin patients might require less than one bag of TAAD solution The actual volume of TAAD solution to be infiltrated is a clinical decision to be made by the surgeon or anesthesiologist. With experience using TAAD, clinicians will acquire a good idea of the effective range TAAD volumes. In very thin patients with little subcutaneous fat the recommended minimum volume of TAAD solution is 500ml. If the volume of TAAD solution is too small, there may be no benefit to TAAD. An insufficient volume of TAAD will exclude the subject from this RCT. Obese patients can to be given up to 2 bags of TAAD solution (2420ml = 2 x 1210ml). The total volume of TAAD solution and the formulation of the TAAD solution must be recorded.

Area Targeted for TAAD

Following TAAD infiltration, the area of tumescence and cutaneous blanching increases over the next 30 minutes. This area ought to include the anticipated surgical incision line plus the surrounding border area having a margin of 10 to 20 cm on each side of the incision site.

Maximum Doses of TAAD Antibiotics: In the present TAAD clinical trial, for any individual patient, the maximum dose of cefazolin is 2,000mg and the maximum dose of metronidazole is 1,000mg. This is equivalent to a maximum dose of two bags (1210ml per bag) of TAAD solution.

Maximum Doses of IV Antibiotic:

The mg dosages of IV antibiotic will conform to community standards of care. Recent publications document that IV antibiotics in obese patients result in sub-therapeutic subcutaneous bioavailability, peak concentration (Cmax) and Time Above MIC (T>MIC). Recent peer-reviewed, evidence based mg-dose recommendations may exceed cefazolin product labeling.

Choice of Antibiotics

Only cefazolin and metronidazole are approved for this TAAD research. For TAAD, all research sites must use the combination of cefazolin with metronidazole. The use of any antibiotics for TAAD other than cefazolin or metronidazole require an approved FDA investigational new drug (IND) application, and must have approval by the over-all principal investigator for this TAAD clinical trial. With FDA and IRB clearance individual research sites may opt substitute one or more different antibiotics for IV antibiotics.

TLA (Tumescent Lidocaine Anesthesia) Formulation

Tumescent anesthetic antibiotic delivery (TAAD) of cefazolin and metronidazole involves the subcutaneous infiltration of a relatively large volume (typically ≥ 1 liter) of dilute cefazolin and dilute metronidazole dissolved in a bag of tumescent lidocaine anesthesia (TLA). The standard TLA solution consists of lidocaine (1gm) and epinephrine (1mg) per 100ml plus sodium bicarbonate (10mEq) per 10ml added to a 1000ml bag of 0.9% physiologic saline or lactated Ringer's solution. This standard TLA formulation results in 1gm of lidocaine in a bag of solution containing 1110ml, which is equivalent to a 1gm/1110ml = 0. 9gm/1000ml = 0.09gm/100ml = 0.09% lidocaine solution. For the present clinical trial, the maximum dosage of tumescent lidocaine cannot exceed **28mg/kg**, with or without general anesthesia (GA). At 28mg/kg of tumescent lidocaine, the risk of exceeding the 6mg of lidocaine per liter of serum (6mg/L) the threshold for mild lidocaine toxicity is 1 per 5,000,000. (**Klein JA, Jeske DR. Estimated Maximal Safe Dosages of Tumescent Lidocaine. Anesth Analg. 2016;122:1350-9**). Patients who do

have significant cardiac, hepatic or renal impairment (ASA class IV or V) are excluded from participating in this TAAD trial.

B. ANCILLARY MEDICATIONS WITH TAAD

From a patient perspective, tumescent infiltration feels odd but it is usually not regarded as "painful". A large majority of patients require no ancillary sedation during tumescent infiltration. If oral or IV sedation is indicated, then consider the following:

Oral clonidine (0.1mg) is an effective antihypertensive and anxiolytic drug. Oral clonidine (0.1mg) also counteracts and minimizes the chronotropic (tachycardia) effects of tumescent epinephrine. Clonidine is usually withheld if the blood pressure is less than 100/60 or pulse is less than 60.

Lorazepam (1mg), by mouth (PO) with or without clonidine, is a useful long acting sedative and anxiolytic drug for patients who are anxious about needles. Lorazepam also has an impressive anti-nausea effect.

Midazolam (1 to 2 mg IM or IV) is rarely required but is used for additional sedation in exceptionally anxious patients.

Atropine (0.4mg IV or IM) is given pre-operatively before infiltration to prevent syncope in patients who have any history of vaso-vagal syncope or near-syncope.

C. INGREDIENTS & FORMULATION OF TAAD SOLUTION:

1. [1000ml] 1L bag of physiologic 0.9% saline or lactated Ringer's solution as solvent
2. [100ml] of 1% Lidocaine (1gm) and Epinephrine (1:100,000) 1mg per 100ml
3. [10ml] Sodium bicarbonate 10 mEq in 10ml
4. [100ml] of Metronidazole, (500mg in a 100ml bag),

Lidocaine (1gram) + Epinephrine (1mg) is available as two 50ml vials (100ml total) of 1% lidocaine with epinephrine 1:100,000.

Cefazolin for injection is available as 1000mg of lyophilized powder per vial.

Metronidazole is available as a water-soluble pro-drug metronidazole phosphate (USP) for parenteral delivery in an iso-osmotic solution containing 500mg metronidazole in 100ml.[119]

D. Method of Preparation of TAAD Solution

Items required to prepare a TAAD solution:

1) ☐ 1 liter bag of 0.9% physiologic saline (sodium chloride) or lactated Ringer's solution
2) ☐ 1 gram of lidocaine and 1milligram of epinephrine in 100ml (two 50ml bottles) of 1% lidocaine and epinephrine 1:100,000.
3) ☐ 10 milliequivalents of sodium bicarbonate in 10ml of 8.4% sodium bicarbonate
4) ☐ 1000mg vial of cefazolin powder
5) ☐ 500mg of metronidazole in a 100ml bag of solution
6) ☐ 30ml syringe and 18gauge needle
7) ☐ Two adhesive safety labels, one attached to each side of the TAAD bag, stating, **"Subcutaneous Tumescent Lidocaine, NOT for IV"**
8) ☐ One label with
   a) name of the patient,
   b) name of physician,
   c) name of person who prepared TAAD solution,
   d) list of the drug in the bag,
   e) date and time of preparation

To Add Cefazolin to TAAD Bag: Cefazolin (1gm) is available has 1gm of lyophilized powder. The cefazolin powder is dissolved by withdrawing 10ml of fluid from the IV bag and injecting it into the

cefazolin vial. After shaking the vial well and allowing a couple minutes for dissolution, the 10ml of cefazolin solution reinjected into the TAAD bag.
To Add Metronidazole to TAAD Bag: Using syringe (30ml or 60ml) and a large gauge needle, transfer 100ml of solution from the 100ml bag of metronidazole to the 1 liter bag of saline.

STEP-BY-STEP PREPARATION OF TAAD SOLUTION:
Using the syringe and hypodermic needle:
1. It may be necessary remove 50ml to 100ml from the 1000ml bag of saline before adding the 100ml of lidocaine, 100ml of metronidazole and 10ml of bicarbonate. The IV bags of some manufacturers may not accommodate the addition of 210ml of fluid.
2. Transfer 100ml of 1% lidocaine with epinephrine 1:100,000 into the IV bag
3. Transfer 10ml of 8.4% sodium bicarbonate into the IV bag
4. Aspirate 10ml of solution from the IV bag into the 30ml syringe and inject it into the vial containing the 1000mg = 1gm of lyophilized cefazolin powder. Shake the vial of cefazolin to promote dissolution of the cefazolin powder. Allow the vial to stand for a minute or two while the cefazolin powder becomes completely dissolved. Aspirate the 10ml of dissolved cefazolin into the syringe and inject it into the IV bag of saline.
5. Using the same sterile syringe and needle, transfer the contents of the 100ml bag of metronidazole solution (500mg) into the of IV bag of solution.
6. Store the newly mixed bag of TAAD solution at room-temperature in a secure environment (for up to 4 hours) until ready for subcutaneous infiltration. If the tumescent infiltration is delayed beyond 4 hours after mixing the TAAD solution, the TAAD bag can be refrigerated and stored for up to 24 hours.

Common Sense Rules for TAAD Preparation
a. Each bag of TAAD solution should be prepared on a clean surface.
b. The preparation and mixture of the tumescent antibiotic delivery (TAAD) solution should be done **within less than 4 hours** of the initiation of the subcutaneous tumescent infiltration. TAAD solution can be stored for 4 hours at room temperature.
c. Only a licensed professional who has received training and instruction in the preparation and mixing of the TAAD should mix and prepare the TAAD solution.
d. During the preparation and mixing of the TAAD solution no one should engage in conversation or in any way distract the person who is preparing the TAAD solution.
e. As each component of the TAAD solution is added to the 1 liter bag of TAAD solution, the person who is mixing and preparing the TAAD solution should audibly and clearly call-out the name of the component being added and check-off the component from the list of components ordered for the TAAD solution.
f. The TAAD solution should not be prepared without legible signed orders written by a physician, physician's assistant or nurse-practitioner.
g. Apply one safety label to each side of the 1 liter bag of saline or lactated Ringer's
h. Apply the label listing the names of the drugs and the name of the clinician to the bag of TAAD solution.

INFILTRATION METHOD FOR TAAD
Subcutaneous infiltration of the TAAD solution can be done in a fully awake and alert patient with minimal discomfort. Rarely is there any need for systemic sedation or analgesia. The painless technique for large volume tumescent infiltration preferably uses devices specifically designed for TAAD. The present clinical trial protocol requires that subcutaneous infiltration of the TAAD solution will be accomplished by using the following specifically designed devices.

HK Tumescent Peristaltic Infiltration Pump: Either an analog HK Surgical peristaltic infiltration pump (HK KIP II) or an HK Surgical digital infiltration pump (HK Tumescent Pump). Both pumps have FDA 510(k) clearance.
HK Infiltration Tubing: disposable single-use sterile tumescent infiltration-pump tubing supplied by HK Surgical.
HK Tumescent Infiltration Cannulas: HK Surgical tumescent infiltration cannulas will be used for infiltration of TAAD solution. The preferred tumescent infiltration cannula for the present TAAD clinical trial is the disposable **HK SubQKath**, a 15cm (6inch) long over-the-needle plastic catheter (similar to IV catheter) with tiny holes distributed over nearly its entire length. For TAAD into subcutaneous abdominal tissue, either a single SubQKath (inserted along the proposed incision line) or two SubQKaths (inserted on each side of and parallel to the proposed incision line) can be used. An alternate tumescent infiltration cannula is the **HK Monty infiltration cannula** (stainless steel, reusable). These devices will have FDA 510(k) clearance, 510(k) exemption or FDA investigative device exemption (IDE).

INFILTRATION TECHNIQUE
The proper tumescent infiltration technique is demonstrated by Jeffrey Klein, MD, on the following YouTube video: ***TAD Tumescent Antibiotic Delivery Abdomen***
https://www.youtube.com/watch?time_continue=9&v=HCGNtXGvjJY

Before inserting the SubQKath through the skin, 1) a small bleb of local anesthesia is injected intradermally at the site of insertion, using a 30gauge needle and 2) the needle of the SubQKath is connected to HK infiltration tubing. The sharp beveled end of the SubQKath needle is inserted into the anesthetized dermis and the KTP peristaltic pump is actuated (started). The initial infiltration or pump rate of the TAAD solution ought to slow to moderate (e.g. a KTP rate of 1.0).

As the needle is advanced through the subcutaneous tissue and fat, while the TAAD solution is simultaneously pumped through the catheter, the tissue becomes anesthetized immediately ahead of the needle tip. In this manner, the insertion of the 6 inch long, 18gauge SubQKath is virtually painless.

After the full length of the SubQKath has been inserted and SubQKath is well positioned, the KTP pump is paused. The hollow needle is withdrawn, leaving the plastic catheter in the subcutaneous tissue. The infiltration tubing is then attached to the catheter hub and the remaining TAAD solution is pumped through the catheter into the subcutaneous tissue. Once the SubQKath has been well placed, the KTP pump rate is increased to a rate of approximately 2.0 to 3.0. The rate can be adjusted to the patient's tolerance.

VIII) Prohibited Medications

Patients who have recently taken any medications at dosages that are likely to significantly impair hempostais or significantly increase the risk of surgical bleeding are excluded**.**

IX) Study Predictor Variables

iv. Methods and Procedures

A. Definitions of Technical Terms, Degree of Obesity:

1. Obesity: BMI ≥ 30 to 40
2. Morbid Obesity: BMI ≥ 40 to 50
3. Super Morbid Obesity ≥ 50

B. Independent Predictor Variables:

The following is a list of data items to be collected prior to, during or after surgery.
1. Patient Routine Demographic Data: Identification, Age, Sex, Height, Weight, BMI, Race

2. Surgeon(s): Name, age, years of post-residency experience, board certification or post-graduate residency status
3. Surgeon's choice of antibiotics to be given by TAAD and by IVAD
4. Surgeon's approximate annul volume of surgical procedures similar to the surgeries performed in the present research.
5. Primary Surgical Diagnosis
6. Surgical Procedure (Open Colon Rectal Surgery, Open Bariatric Surgery, etc.)
7. Total Dosages of all General Anesthetic Agents
8. Use of and type of subcutaneous sutures
9. Material used for seromuscular suturing
10. American Society of Anesthesiologists (ASA) status.
11. List of Significant Medical Problems and Co-Morbidities (Endocrine/Diabetes, Hypertension, Cardiovascular, Pulmonary, Renal, GI, etc)
12. Concurrent Drugs & Dosages
13. Immune Status (Diabetes mellitus, Chemotherapy, Radiation therapy, Corticosteroid or other immunosuppressive therapy, HIV status, etc)
14. Steroid (glucocorticoids) name, dosage and duration of use
15. Immunosuppressant drug use (non-steroidal): name, dosage duration of use
16. Drug(s) known to significantly affect hemostasis (platelet function inhibitors, aspirin, ibuprofen, clopidogrel, heparin, etc).
17. Drug Allergies
18. Occurrence of Concomitant antibiotic IVAD prophylaxis (appropriate/adequate or inappropriate/inadequate according to CDC guidelines)
19. Taking any drug(s) known to interfere with the metabolism of lidocaine, cefazolin or metronidazole or to adversely interact with these drugs (Erythromycin, Clarithromycin, ketoconazole, fluconazole, sertraline (Zoloft), ciprofloxacin.
20. History of radiation therapy involving the area near the proposed incision site
21. Intraoperative hypotension or hypertension
22. Intraoperative hypothermia
23. Operative time: incision-to-close
24. Abdominal Wound Class: Clean, Clean-Contaminated, Contaminated, Dirty (See Appendix)
25. Number of times per day that incision site is washed with soap and water
26. Thickness of midline abdominal subcutaneous fat (estimated prior to tumescent infiltration) measured by ultrasound if available.
27. History of Smoking
28. Any condition with significant risk of surgical site wound infections
29. List of Prior Surgeries
30. Pre-existing or Concurrent Infections (cutaneous, urinary, pneumonia are exclusionary)
31. List of measures for preventing VTE actually employed for each individual subject
32. Psychological Diagnoses, major depression, psychosis, anxiety disorder.
33. Presence and duration of prolonged wound drainage
34. Time of completion of the IVAD will be classified into the following groups:
    a) IVAD completed more than 60 minutes prior to incision
    b) IVAD completed more than 30 minutes and less than 60 minutes prior to incision
    c) IVAD completed before incision and less than 30 minutes prior to incision
    d) IVAD after incision and during the surgery
    e) IVAD after the surgical closure
    f) No IVAD

X) Study Outcome Measures: Definitions

A. Outcome Variables:

Primary Outcome Variable:

Diagnosis of SSI within 30 days of surgery (Binary Data). Surgical site infection is defined by the CDC criteria (see iv B above).

Secondary Outcome Variables:

1. Diagnosis of Venous Thromboembolism (VTE) including deep vein thrombosis (DVT) or pulmonary embolism (PE) within 30 days of surgery. The definition and diagnostic criteria for VTE and routine methods of VTE prophylaxis used by each research site will be recorded. The method of diagnosis of VTE may vary among research sites. But within any given site the diagnostic methods should be consistently the same.
2. Diagnosis of Sepsis or
   Diagnosis of Systemic Inflammatory Response Syndrome (SIRS)

Other Outcome Variables

1. ICU admission (or equivalent unit) and number of hours in ICU
2. Length of Stay (LOS) in hospital after surgery (hours)
3. Time in post-operative/post-anesthesia recovery unit (hours).
4. Time from arrival in post-op recovery to time of ambulation (hours).
5. Post-Op Narcotic Requirements (total mg and mg/kg)
6. Unexpected re-admission to hospital (for any reason) ≤ 30 days of surgery (Binary Data)
7. General Anesthesia Requirements (Minimal Alveolar Concentration)
8. Diagnosis of C. Difficile colitis

B. Surgical Wound Classification (Overview): Definition of SSI is subdivided into three subsets.

Superficial Incisional SSI is defined as an infection within 30 days of surgery involving skin or subcutaneous tissue

Deep Incisional SSI is defined as an infection within 30 days after surgery without an implant or 1 year if an implant is left in place and the infection appears to be related to the surgery and the incision involves fascia and muscle layers

Organ/Space SSI is defined as an infection occurring within 30 days of surgery without an implant or 1 year if an implant is left in place and the infection appears to be related to the surgery and the infection involves any organs or spaces opened and manipulated during the surgery

The following criteria for a diagnosis of SSS are listed in CDC Guideline for Prevention of Surgical Site Infection, 1999. Guideline for Prevention of Surgical Site Infection, 1999. www.cdc.gov/ncidod/dhqp/pdf/guidelines/SSI.pdf

DETAILED CRITERIA FOR DEFINING A SURGICAL SITE INFECTION (SSI)

Superficial Incisional SSI:

Superficial Incisional Infection is defined as an infection that occurs within 30 days after the operation, where the 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
A Deep Incisional Infection is defined as an infection that occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place & the infection appears related to the surgery
and
the infection involves deep soft tissues (e.g., fascial and muscle) 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 dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or
symptoms: fever (>38ºC), 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 organ space SSI.

Organ Space SSI
An Organ Space SSI is defined as an infection that occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place & infection appears related to the operation
and an infection that involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation
and **at least one** of the following:
1. Purulent drainage from a drain that is placed through a stab wound into the organ/space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

XI) Statistical Plan

Approximate Number of Subjects
Multicenter Center Trial: . For a statistical power of 0.8, the required sample size is approximately 660 patients with the potential for early stopping for efficacy after 330 patients. Group sequential analysis with one intermediate stopping point will be used.

L. Data Monitoring Committee: Data will be monitored by the Clinical Trials Statistics Collaboratory, Department of Statistics, University of California, Riverside, CA

- Daniel Jeske PhD, Chair, Department of Statistics, UCR
- Clinical Trial Coordinator: To be determined

Additional members of the Data Monitoring Committee may include selected physicians as well as graduate students and faculty in the UCR Medical School or the UCR Department of Statistics, University of California, Riverside, will compose the data monitoring committee to assure the safety of the subjects. The statistical design of this trial includes **periodic group sequential analysis** (with one stopping point) to allow early termination of the study in the event of early stage statistical significance.

M. Clinical Oversight Committee:

- There will be an **Independent Clinical Oversite Committee** that will monitor the clinical data, protocol compliance and all reports of adverse outcomes.
- A group of **Trial Site Principal Investigators** will periodically review the clinical data, protocol compliance and any reported adverse outcomes and confer with the Data Monitoring Committee and the Clinical Oversite Committee.
- At each clinical research site the Sub-Principal Investigator will be responsible for assuring the safety of the subjects at that site.

N. This is a controlled open label randomized clinical trial (RCT):

- This trial is a randomized clinical trial of the Tumescent Antibiotic Delivery plus Intravenous Antibiotic Delivery (TAAD+IVAD) versus IVAD alone.
- Because of the nature of tumescent infiltration, it is not possible to mask the treatment assignment. The patient and the clinician who delivers the TAAD infiltration cannot be "blinded" to the treatment assignment.
- A different clinician, other than the surgeon, will do the clinical evaluations looking for surgical site infections (SSI).

O. Statistical Analysis, Power Calculations and Samples Size Estimation

Daniel Jeske PhD and **Joyce Fu, PhD**, Department of Statistics, University of California, Riverside helped design the statistical analysis for the present clinical investigation. We will use group sequential analysis with one stopping points. Using balanced treatment allocation, assuming the incidence of surgical site infection in the targeted population is 0.14 and an anticipated effect size of 50 percent at a two-sided level of significance (alpha) of 0.05 and a power of 0.8, the estimated sample size for the TAAD RCT is either 330 (at first stopping point with 165 control=IVAD and 165 treatment =IVAD+TAAD) or 660 patients.
See TAAD Sample Size Estimate, attached as an appendix.

P. Treatment Assignment and Randomization

Only after having obtained appropriate informed consent from the patient will the patient be randomly assigned to a treatment.
All patients will receive IVAD of cefazolin. The dose of IV cefazolin may vary from one research site to the next depending on the research site's standard IV dose of cefazolin for SSI prevention.

At each research site, the dose of IV cefazolin will be the standard IV cefazolin dose routinely employed at that research site. Any research site may elect to also give IV metronidazole 500mg as part of that site's routine IVAD for the TAAD protocol.

The timing (30 to 60 minutes prior to surgical incision) and mg/kg dosage of IVAD antibiotic will conform to accepted CDC Guidelines for SSI Prophylaxis and the hospital policies.

In this study, patients will be randomly assigned to one of 2 treatment groups:
• Control group (IVAD) will receive IVAD only [50% of patients]
• Treatment group (TAAD+IVAD) will receive both TAAD and IVAD [50% of patients],

Each bag of TAAD solution contains 1gm cefazolin and 500mg metronidazole.
The antibiotic dose in the IVAD alone is the same as the IVAD dose with IVAD+TAAD

The following method of balanced random assignment for an open-label design assures that the intended proportion of patients will be assigned to the respective treatment groups. For example, at a given research site, if there have been 4n patients enrolled within a set of matched patients, then
2n patients will be assigned to receive control treatment IVAD and
2n patients assigned to receive treatment TAAD+IVAD.

Balanced randomization will be physically accomplished by assignment determined by flipping a fair coin. The person who performs the following randomization task should not be a surgeon or a member of the surgical team. Specifically, by way of example, if a research site expects to enroll 24 patients, then
1) 24 envelops and 24 cards (5x7 inch) are labelled sequentially from 1 to 24.
2) Place each card inside the correspondingly numbered envelope.
3) Separate the envelops-cards into sets of four each: {1,2,3,4}, {5,6,7,8},…,{21,22,23,24}.
4) Select a set of 4 envelops, and remove a card from one of the envelopes.
5) Flip the coin:
    a) If the coin shows heads then write IVAD on the chosen card
    b) If the coin shows tails write IVAD + TLD on the card
    c) After 2 patients have been assigned to IVAD then the remaining card(s) will be assigned to IVAD+TAAD.
    d) Thus, with each group of 4 cards, exactly 2 cards will be randomly assigned to IVAD and 2 cards will be randomly assigned to IVAD+TAAD.
6) Fold each of the cards once, with the written assignment obscured from view, then replace each card into its corresponding envelope and seal all four envelops.
7) Repeat this sequence until all 24 cards-envelops have been given a treatment assignment.
8) Arrange the envelops into numerical order
9) On the day of a subject's surgery, after the patient has signed the informed consent and the patient has been screened and determined to conform to all of the inclusion criteria, but none of the exclusion criteria, the next envelop in the sequence (the envelop having the lowest number) is assigned to the patient. (In general, treatment assignment should not be made more than 12 hours prior to surgery in order to avoid possible confusion if the surgery were to be cancelled.
10) The assigned envelop is opened by a clinician, the treatment indicated on the card is assigned to the patient and the appropriate orders for IVAD alone or IVAD +TAAD will be formally written on the hospital's routine pre-operative order form(s).
11) If the card indicates TAAD+IVAD then an assigned research-team member will personally supervise and witness the preparation of the TAAD solution or personally mix the bag(s) of

TAAD solution. Each bag of TAAD solution will be labeled (front and back) with HK Safety Labels, which state "NOT for IV USE"
12) The patient's name is written on the card. A digital photo of the card is taken. The card is filed in a secure (locked) location for future reference.
13) The patient's name, date of randomization and treatment assignment are recorded on a confidential master list containing the names of all subjects and corresponding treatment assignments.
14) The master list of patients and individual treatment assignments will be emailed to the PI and the Safety monitoring committee after every subject has been entered into the clinical trial.
15) Alternatively, depending on future funding, we might institute an iPad based randomization process with features similar to those described above.

XII) Safety monitoring

H. Safety of TAAD: Among the secondary outcome variables are any adverse event (AE) associated with TAAD. It is our intention to document the incidence of any adverse events associated with the TAAD Clinical Trial and the TAAD infiltration process involving the SubQKath infiltration catheter, and peristaltic tumescent infiltration pump & tubing.

The following TAAD safety assessment check list is to be completed between 24 to 36 hours after TAAD infiltration. Please indicate (below) if any of the following signs and symptoms of appear within the first 24 hours after surgery:

Adverse Events (AE) during TAAD Trial 170701

Problems: Check One Answer per Problem		Grade 1 None		Grade 2 Mild/Moderate		Grade 3 Severe		Grade 4 Life-Threatening
1. DERMATOLOGIC								
Bruising		None		At TAAD site		Excessive, Unusual		NA
Petechiae		None		At TAAD site		Generalized, Widespread		NA
Pruritus		None		At TAAD site		Generalized, Widespread		NA
Induration, Swelling		None		At TAAD site		Generalized, Widespread		
Pain or Tenderness		None		At TAAD site		Excessive, Unusual		NA
Rash, Erythema		None		At TAAD site		Diffuse		NA
Rash, Eczematous		None		At TAAD site		Diffuse		NA
Rash, Maculopapular		None		At TAAD site		Diffuse		NA
Rash, Bullous		None		At TAAD site		Stevens-Johnson		Toxic Epidermal Necrolysis
Cellulitis		None		Only PO Antibiotics		IV Antibiotics		Sepsis, Tissue Necrosis
Necrotizing Fasciitis		None		NA		Limited to TAAD Site		Sepsis, Widespread Necrosis
2. CARDIOVASCULAR								
Thrombosis or Pulmonary Embolism (PE)		No Symptoms		Symptoms & No intervention indicated		Symptoms & Intervention indicated		Life-threatening PE
Arrhythmia		No Symptoms & No intervention		No Symptoms & No urgent intervention		Symptoms & No urgent intervention		Life-Threatening Arrhythmia
Hypertension		≤ 160/100		160/100 to 180/110		> 180/110		Malignant Hypertension

Hypotension		No Symptoms		Requires PO fluids		IV fluids needed		Shock
Cardiac Ischemia/MI		NA		NA		+ Tests or Symptoms		Unstable or Acute MI
Congestive Heart failure (CHF)		No Symptoms		Symptoms upon exertion		Symptoms at rest, Needs Oxygen		Life Threatening, Urgent Intervention
Vasovagal Reaction		None		Near syncope		Syncope		
Hemorrhage		NA		No transfusion		Transfusion≤2units PRBC		> 2units Packed RBC (PRBC)

3. ALLERGIC REACTIONS

Anaphylaxis		None		NA		Gradual Onset		Immediate Onset
Angioedema		None		No Airway Involvement		Mild Airway Involvement No Intervention Required		Threatened Complete Airway Obstruction

4. GI

diarrhea		None or Minimal		≥ 3 to 6 over baseline		≥ 7 stools in 24 hours		Massive, Life-threatening
nausea		Transient		Persistent, Decreased oral intake 24-48 hrs		Minimal Intake ≥24-48 hrs, Requires IV Fluids		Life-Threatening, Hypotensive Shock
Vomiting		None to Minimal, Able to Eat		Frequent, Mild Dehydration		Persistent, Requires IV Fluids		Life-Threatening, Hypotensive Shock
Acute Pancreatitis		None		Mild, Amylase Elevated		Moderate, Significant Pain		Severe or Life-Threatening
Acute Hepatitis		None		Elevated Liver Function Tests		Clinical Jaundice		Hepatic Failure

5. MUSCULOSKELETAL

Arthralgia, Arthritis		None		Mild, No Interference with Activities		Moderate, Interfers with Normal Activities		Severe, Unable to do Self-Care
Myalgia, Muscle Pains		None		Mild, No Interference with Activities		Moderate, Interfers with Normal Activities		Severe, Unable to do Self-Care

6. NEUROLOGIC

Circumoral/Tongue numbness		None		Mild to Moderate		Severe		Not Applicable N/A
Double/Blurred Vision		None		Mild to Moderate		Severe		N/A

Muscle Twitching		None		Mild to Moderate		Severe		N/A
Altered Mental Status		None		Mild Lethargy, Somnolence		Confusion, Memory Impairment		Delirium, Obtundation, Coma
Ataxia		None		Detectable, Normal Activities		Moderate, Interferes with Normal Activities		Severe, Unable to do Self-Care
Headache		None		Mild, Doesn't Interfere with Activity		Moderate, Interferes with Activity		Severe, Unable to do Self-Care
Weakness Neuromuscular		None		Mild, Doesn't Interfere with Activity		Moderate, Interferes with Activity		Severe, Unable to do Self-Care, or Affects Breathing
Seizures		None		NA		1 to 3 Seizures		Prolonged Seizures, Refractory to Treatment
Syncope		None		Mild, Vaso-Vagal Near Syncope		Loss of Consciousness, No Treatment Required		Loss of Consciousness, Requires Treatment
7. RENAL								
Chronic Renal Insufficiently		None		Na Restriction, eGFR 59 – 30 ml/min/1.73m2		May Need Dialysis. eGFR 29 - 15 ml/min/1.73 m2		Needs Dyalisis or Renal Transplant
Post-Op Evaluation of Serum Creatinine		None		Minimal		Moderate		Severe
Acute Post-Op Renal Failure		None		Creatinine: (1.5x – 2x) > baseline		Needs Temporary Dialysis		Permanent Dialysis
8. RESPIRATORY								
Acute Bronchospam		None		Mild Symptoms, No treatment Requires		Moderate, Requires Treatment		Severe, Possibly Requires Intubation
Dyspnea		None		Dyspnea on Exertion		Dyspnea at Rest		Respiratory Failure, Requires Intubation
9. SENSORY								
Hearing Loss		None		Mild, No Treatment Required		Moderate, Interferes with Activity		Profound Bilateral Hearing Loss

Tinnitus		None		Mild, No Treatment Required		Moderate, Interferes with Activity		Severe, Prevents Normal Activities
Vertigo		None		Mild, No Treatment Required		Moderate, Interferes with Activity		Severe, Prevents Normal Activities

10. SYSTEMIC

Chills		None		Mild, No Treatment Required		Moderate, Interferes with Activity		Severe, Prevents Normal Activities
Fatigue Malaise		None		Mild, No Treatment Required		Moderate, Interferes with Activity		Severe, Prevents Normal Activities
Fever C◦		≤ 38.6		38.6 - 39.3		39.4 - 39.9		≥ 40

11. LABORATORY VALUES: (Compared to Baseline Prior to TAAD)

ALT SGPT		Upper Limits of Normal (ULN) = 40 units/L		< 5 x ULN		5 - 15 x ULN		Severe Hepatitis >15 x ULN
AST SGOT		56 units/L =ULN		< 5 x ULN		5 - 15 x ULN		Severe Hepatitis >15 x ULN
Amylase & Lipase		140units/L =ULN & 160units/L = ULN		2 x ULN & 2 x ULN		4 x ULN & 4 x ULN		Life Threatening Pancreatitis

12. HEMATOLOGIC

WBC		Within Normal Limits or Borderline		<4000/mm3		Severe Leukopenia < 1000/mm3		Life Threatening <500/mm3
Absolute Neutrophil Count		Within Normal Limits or Borderline		NA		Severe Neutropenia		Life Threatening Neutropenia
Platelet Count		Within Normal Limits or Borderline		NA		Significant Thrombo-cytopenia		Life Threatening Thrombo-cytopenia

AE Not Otherwise Specified

XIII) Stopping rules for patients

In the setting of a clinical trial involving ongoing or repeated treatements, if a significant trial-related adverse event (AE) occurred, then the affected subject's participation in the trial would have to be stopped.

The present TAAD trial simply involves a a single treatment, tumescent infiltration of the TAAD solution. If a significant AE were to occur during the infiltration, then the infiltration would stopped and the patient's participation would be stopped. If a significant AE, possibly related to TAAD infiltration, were to occur after the TAAD infiltration has been completed, then the the subject's ongoing clinical condition would be documented; and the patient's participation would not necessarily have to be stopped.

XIV) Stopping rules for the study

There will be a data monitoring committee that will decide, based on clinical data, whether or not any accumulated history of excessive AE's is sufficient criteria to terminate the trial.
The statistical design of the TAAD trial involves group sequential analysis with one stopping point. The study will be stopped midway at the first stopping point if there is a significant difference in SSI risk between treated and not treated group. The study could also be stopped if one treatment was so dramatically better than the other, that it would be unethical to continue the trail.

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