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170515 Protocol TAAD RCT

**Title:**

**Tumescent Anesthesia Antibiotic Delivery (TAAD) and SubQKath for Prevention of Surgical Site Infection, Thrombosis and Sepsis.**

**WIRB Protocol #** pending FDA IND approval

**Client's Identifying Number:** TAAD

**Clinicaltrials.gov Registration #** pending FDA IND approval

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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, ertapenem, lidocaine, epinephrine. Possibly ertapenem and other appropriate antibiotics.

There will be more than one or more research site(s).

ii. **Purpose of Study and Background**  
**A. Objectives and purpose of the present study.**

Despite the use of multiple interventions, surgical site infection (**SSI**) continues to be a significant problem. There is a need for an effective, accessible, inexpensive, simple, safe technique that reduces the risk of SSI. Intravenous antibiotic delivery (**IVAD**) using an over-the-needle intravenous (**IV**) catheter is the current standard mode of antibiotic delivery for SSI prevention.

- 1) Subcutaneous delivery of an antibiotics such as cefazolin and metronidazole is off-label.
- 2) Subcutaneous infiltration of dilute a tumescent lidocaine solution (with or without antibiotics) at lidocaine dosages that exceed 7mg/kg is off-label.
- 3) Subcutaneous infiltration of dilute antibiotic(s) in a tumescent lidocaine solution using a novel over-the-needle subcutaneous catheter (SubQKath) requires FDA 510(k) approval.

This multicenter randomized clinical trial (**RCT**) protocol is designed to

- 1) compare two modes of antibiotic delivery,
- 2) validate the safety of tumescent lidocaine at dosages up to 28mg/kg,
- 3) validate the safety of the SubQKath for tumescent anesthetic antibiotic delivery (**TAAD**).
- 4) This protocol is not a clinical trial comparing the effects of different drugs.
- 5) This RCT compares IVAD alone versus concomitant TAAD and IVAD (**TAAD+IVAD**).

TAAD using a novel over-the-needle subcutaneous catheter (SubQKath) by direct subcutaneous infiltration of dilute antibiotic(s) in a tumescent lidocaine solution is a novel mode of antibiotic delivery.

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.

We hypothesize that, compared to IVAD alone, TAAD+IVAD will be superior in terms of reducing the risk of SSI, as well as venous thromboembolism (**VTE**) and systemic inflammatory response syndrome (**SIRS**).

Tumescent infiltration (**TI**) drug delivery involves subcutaneous infiltration relatively large volumes (1 to 2 liters or more) of a relatively dilute solution of epinephrine ( $\leq 1$ mg) 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 infiltration (TI) Solution functions as a drug delivery vehicle. Tumescent infiltration (TI) drug delivery is a mode of drug delivery that has a pharmacokinetic profile distinct from intravenous (IV), intramuscular (IM), oral (PO) or transcutaneous delivery.

When a TI Solution is used as a vehicle to deliver lidocaine subcutaneously we have TI solution + Lidocaine = tumescent lidocaine anesthesia (**TLA**).

Further, when an antibiotic is added to a TLA solution, TI Solution + Lidocaine + Antibiotic, the result is a tumescent anesthetic antibiotic delivery (TAAD) solution.

TAAD drug delivery overcomes two common types of antibiotic toxicities: total (mg) dose-related systemic toxicity and concentration-related (mg/L) local-tissue toxicity.

TI drug delivery provides

- 1) high, prolonged (12 to 18 hours or more) localized subcutaneous drug concentrations,
- 2) slow steady systemic (serum) drug delivery having a concentration-time profile similar to a slow constant IV infusion and

3) a peak serum drug concentration that is substantially less than would be expected by routine doses given by IV delivery.

TAAD has the potential to prevent or overcome an antibiotic-resistant infection of subcutaneous tissue using less than the usual total mg IV dose of an antibiotic while providing higher subcutaneous antibiotic concentrations than can be achieved by IV delivery, and simultaneously avoid systemic antibiotic toxicity by limiting the rate of systemic antibiotic absorption and thus minimizing the peak antibiotic serum concentration.

For example, TAAD delivery of an aminoglycoside antibiotic has the potential to provide subcutaneous antibiotic concentrations that are sufficiently dilute to avoid local tissue toxicity while simultaneously providing subcutaneous antibiotic concentrations that are significantly higher than can be achieved by IV delivery, with a reduced risk of systemic (ear or kidney) toxicity.

The present research protocol, only allows the use of antibiotics that have FDA approval. Cefazolin and metronidazole have FDA approval and are known to be safe and effective when delivered by subcutaneous infiltration as documented by published reports in peer-reviewed literature. A clinical trial using subcutaneous delivery of a TAAD solution containing cefazolin and metronidazole requires Division of Anti-Infective Products (DAIP) approval of an investigational new drug (IND) application.

Tumescent dilution reduces the potential for subcutaneous, concentration dependent tissue toxicity while simultaneously providing subcutaneous drug concentrations that are significantly higher than can be achieved by IV or any other mode of systemic drug delivery. For antibiotics, the therapeutic benefits of IV delivery are muted by the fact that IV delivery often results in sub-therapeutic subcutaneous antibiotic concentrations and the associated increased risk of developing drug resistance. For some cutaneous infections and for preventing surgical site infections, tumescent infiltration drug delivery overcomes these limitations of IV delivery.

### **Scientific Generalizability**

This protocol is not a clinical trial comparing the effects of different drugs. This clinical trial protocol is designed to compare two modes of antibiotic delivery.

In order to maximize the generalizability of the results of this research, the protocol is designed to accommodate a wide variety of clinical situations encountered internationally. The protocol provides for the inclusion of 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.

Research sites will be provided with sufficient supply of devices (SubQKaths, tumescent lidocaine anesthesia (TLA) peristaltic pump and tubing) to facilitate efficient TAAD infiltration.

For the purposes of scientific validity and generalizability, this research intentionally does not restrict the choice of generic antibiotic to that of a single specified manufacturer. This protocol explicitly allows the use of any generic version of the antibiotic, irrespective of the manufacturer. This protocol also allows TAAD of an antibiotic that is only available as a branded (non-generic) drug.

In some cases, the principal investigator (PI) will supply individual research sites in medically indigent communities with a TAAD Drug Kit containing antibiotics, lidocaine with epinephrine, sodium bicarbonate and 1 liter bags of a balanced salt solution.

For the purpose of statistical analysis and validity, for any given subject, the same antibiotic(s) will be used for both TAAD and IVAD.

Within any individual research site, it is preferred that the antibiotic formulation, source and brand will be standardized and invariant, subject to continued availability of the antibiotic.

### **“Off-Label” Aspects of Tumescant Drug Delivery**

The use of TAAD involves:

- 1) subcutaneous antibiotic delivery which is “off-label” for most FDA-approved antibiotics,
- 2) unapproved drug formulations (more dilute tumescant anaesthesia antibiotic delivery (TAAD) solution)
- 3) new unapproved (28mg/kg) recommended maximum dosages for tumescant lidocaine.

### **Primary and Secondary End Points**

This protocol is designed to prospectively collect data to evaluate the efficacy and safety of the TAAD mode of subcutaneous antibiotic delivery.

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

The primary end-point is the incidence of surgical site infections (SSI). The protocol compares TAAD + IVAD with IVAD alone with respect to:

- 1) the incidence of SSI,
- 2) the incidence of post-operative venous thromboembolism (VTE) and
- 3) the incidence 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) for the tumescant drug delivery, tumescant peristaltic pumps and tumescant infiltration tubing.

**Definitions:** Tumescant anesthesia antibiotic delivery (**TAAD**) is defined as the subcutaneous infiltration of a dilute solution of antibiotic(s) in a solution of tumescant lidocaine anesthesia (**TLA**). TLA consists of a dilute solution of lidocaine ( $\leq 1\text{gm/L}$ ), epinephrine ( $\leq 1\text{mg/L}$ ) and sodium bicarbonate ( $10\text{mEq/L}$ ) in 0.9% physiologic saline or lactated Ringer’s solution. Our estimated maximal safe dosage of TLA lidocaine is 28mg/kg without liposuction.

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

**The Principal aim** of the present research is to compare two methods of antibiotic delivery:

- 1) concomitant TAAD and IVAD (TAAD+IVAD) versus
- 2) IVAD alone (IVAD),

with respect to the prevention of SSI. The IV doses of antibiotics will be equal for IVAD alone and for TAAD + IVAD.

The focus of this research project is on preventing 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.

The target populations for the present clinical trial are patients who have a high risk of SSI. These 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.

**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).

**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.

### **Primary Outcome Variable**

Surgical Site Infection (detected within 30 days of surgery): 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. Time in post-operative/post-anesthesia recovery unit.
4. Time from arrival in post-op recovery to time of ambulation).
5. Post-Op Narcotic Requirements (total mg and mg/kg)
6. Unexpected re-admission to hospital (for any reason)  $\leq$  30 days of surgery (Binary Data)
7. General Anesthesia Requirements (Quantitative Measure)
8. Diagnosis of C. Difficile colitis

## **B. Background:**

**1) Risk of SSI Colorectal Surgery.** Surgical site infections (SSIs) are a high priority target of hospital quality improvement efforts<sup>1</sup>.

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 GI surgery range from less than 1% to 15% for routine elective GI surgical procedures to approximately 20% to 30% for surgeries defined as contaminated or dirty.<sup>2</sup> The incidence of incisional SSI in colon perforation with generalized contamination can be as high as 82% compared to a 25% incidence with colon perforation with localized contamination.<sup>3</sup> 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.<sup>4</sup> Among obese colectomy patients the risk of SSI is increased by 60%.<sup>5</sup> Low concentrations of antibiotic within peri-incisional tissue is a significant risk factor for SSI in colorectal surgery.<sup>6</sup>

A significant percentage of SSIs becomes apparent after hospital discharge.<sup>7</sup> Retrospective diagnosis of SSI is inaccurate.<sup>8</sup> 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.** The Centers for Disease Control (CDC) 1999 consensus guidelines for SSI antibiotic prophylaxis is the worldwide standard of care<sup>9</sup>. 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%<sup>10 11</sup>. 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<sup>12</sup>. 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.<sup>13</sup>

### **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<sup>14</sup>. 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) 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.

### **5) Obesity Impairs Subcutaneous Bioavailability**

Obesity increases the risk of SSI<sup>15</sup>. 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 22% that of normal subjects. In obese patients, the subcutaneous penetration of cefoxitin after IVAD was less than 10% in 8 of 10 patients<sup>16</sup>.

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<sup>17</sup>.

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<sup>18</sup>.

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)<sup>19</sup>. 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.

## 6) 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.

Because the efficacy of a mode of antibiotic delivery is proportional to the cumulative antibiotic exposure within the targeted tissue, TAAD ought to 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 produce 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.

## 7) Tumescent Infiltration

TAAD infiltration involves the subcutaneous infiltration of antibiotics in a relatively large volume (typically ≥ 1 liter) of dilute antibiotics dissolved in a solution of tumescent local anesthesia (TLA) consisting of lidocaine (<1gm/L), epinephrine (<1mg/L), sodium bicarbonate (10 mEq/L) in physiologic saline. Painless infiltration of a liter or more of TAAD solution without significant sedation or systemic analgesia requires training, skill and medical devices specifically designed for TAAD. The efficiency of infiltrating a large volume of TAAD solution is improved with the use of specialized tumescent infiltration cannulas (HK SubQKath), peristaltic infiltration pump (HK TLA Pump) and infiltration tubing (HK infiltration tubing).

## 8) Subcutaneous Metronidazole

Dilute metronidazole is safe for subcutaneous infiltration.<sup>20 21</sup> Metronidazole is available as a water-soluble pro-drug metronidazole phosphate for parenteral delivery in an iso-osmotic solution containing 500mg metronidazole in 100 ml<sup>22</sup>.

Although the FDA approved labeling for metronidazole does not mention subcutaneous infiltration, this mode of delivery has been used with success. 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 resulting SSI rate was 66.6% (20/30) with saline irrigation of the incision site versus 26.6% (8/30) with subcutaneous infiltration of metronidazole (P < 0.01). There were no adverse drug reactions attributable to subcutaneous infiltration of metronidazole<sup>23</sup>.

TAAD-metronidazole infiltration involves the subcutaneous infiltration of a relatively large volume of tumescent metronidazole (approximately 500mg/bag of TAAD solution, and up to 2 bags obese patients).

### 9) Subcutaneous Cefazolin

Subcutaneous delivery of dilute cefazolin is recognized as a safe procedure.<sup>24</sup> For some surgeons it is common practice, to inject cefazolin 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. Although "off-label", this procedure is considered safe, but probably inefficient 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. When the cefazolin package insert was written in the early 1970's, subcutaneous delivery was not discussed. The goal of antibiotic delivery was to achieve rapid 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.

### 10) TAAD Benefits

The antibiotic solution for TAAD produces an intense 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<sup>25</sup>. 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<sup>26 27 28</sup>.

Lidocaine is known to be bactericidal thus 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.<sup>29 30</sup>

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. Thus TAAD can be expected to decrease requirements of general anesthetic agents and post-operative narcotic analgesics and also facilitate earlier post-operative ambulation.

### 11) TAAD May Reduce Thromboembolism and Blood Viscosity

The leading cause of death associated with liposuction under general anesthesia is pulmonary embolism<sup>31</sup>. In contrast, the incidence of venous thromboembolism following tumescent liposuction totally by local anesthesia is virtually zero.<sup>32</sup> This remarkable dichotomy might be explained by the antiplatelet activity of lidocaine in tumescent local anesthesia (TLA). It is known that lidocaine inhibits platelet function<sup>33 34</sup>. There is evidence that lidocaine may reduce the risk of post-operative thromboembolism<sup>35 36 37</sup>. Our data from an on-going clinical trial among liposuction patients suggests that in-vivo systemic platelet function is significantly reduced after infiltration of TLA and the platelet inhibition persists in the postoperative period<sup>38</sup>. 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%<sup>39</sup>. In general, colorectal surgery patients have a risk of VTE of 1.6% to 2.4%.<sup>40 41 42</sup> TAAD may reduce the risk of VTE. Another study found that colorectal surgery for cancer had a risk of VTE as high as 16%<sup>43</sup>.

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<sup>44</sup>. In contrast, with tumescent liposuction totally by local anesthesia, this percentage total blood in the aspirate is approximately 1 to 2 percent.<sup>45</sup>

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.

## 12) TAAD Infiltration: Timing & Technique

The timing of TAAD is not as critical as is the timing of IV antibiotic delivery. Current SSI prophylaxis guidelines mandate a 30 minute 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<sup>46 47 48 49</sup>.

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<sup>50</sup>.

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 gentleness and attention to detail.

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. Oral clonidine (0.1mg) is an effective anxiolytic that minimizes the chronotropic effects of epinephrine. Clonidine is withheld if the blood pressure is less than 100/60 or pulse is less than 60. Oral lorazepam (1mg), with or without clonidine, is also effective for patients who are anxious about needles. Rarely is

midazolam (2 mg IM or IV) required. Atropine (0.4mg IV or IM) can be given before infiltration to prevent syncope for patients who have any history of vaso-vagal syncope or near-syncope..

When TAAD is completed before entering the operating room (OR), the infiltration process does not interfere with the OR work-flow nor does it prolong the total time in the OR. Alternatively, TAAD infiltration can be performed under general anesthesia. When TAAD is done in the OR the infiltration procedure may consume expensive operating-room time, add to the logistic burden of a busy operating room staff and delay the incision.

### **Detumescence**

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<sup>51 52</sup>.

### **iii. Criteria for Subject Selection**

#### **A. 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. See statistical analysis for sample size estimates and power analysis).

#### **B. Gender of Subjects**

This study will involve both males and females.

#### **C. Age of Subjects:**

Participating volunteer patients must be at least 18 years old.

Pediatric patients will only be enrolled with FDA IND approval.

#### **D. Racial and Ethnic Origin**

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

#### **E. 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.
- 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.** This study will involve both males and females
- 5.** Patients in ASA (American Society of Anesthesiology) class (I or II or III or IV) will be included.
- 6.** For each patient, the wound classification, ASA classification, trauma and burn classification will be carefully recorded. Abdominal wound classifications: Clean-Contaminated, Contaminated, or Dirty are eligible to participate.
- 7.** Patients must be appropriately screened for the proposed surgery.

## **F. Choice of Antibiotics**

This is not a clinical trial of antibiotics; rather this is a clinical trial comparing two modes of antibiotic delivery. Each individual research site must consistently use the same antibiotics.

All research sites are encouraged to use cefazolin alone or both cefazolin and metronidazole for TAAD and IV antibiotic delivery.

For TAAD, individual research sites will have the option to use cefazolin alone or both cefazolin and metronidazole. With appropriate FDA and IRB clearance, an individual research site may use a water-soluble antibiotic, other than cefazolin or metronidazole, for TAAD. Such an antibiotic must not have any known risk of causing irritation or tissue toxicity with subcutaneous injection. Other antibiotics that have been cleared by the FDA for subcutaneous infiltration may be used in TAAD.

For IVAD, an individual research site must consistently use the same antibiotic combination. The preferred combinations are cefazolin alone or cefazolin with metronidazole. If an antibiotic other than cefazolin and metronidazole is used for IVAD alone, then the compatibility of the antibiotic combination must be well established and pre-approved by the FDA.

## **G. 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 for individual research sites. 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.

## **H. 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  $\geq$  ASA 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.

#### I. Vulnerable Subjects are excluded

1. Pregnant women

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

3. Children < 18 years of age, unless there is explicit FDA approval of participation of pediatric patients.

#### iv. Methods and Procedures

##### A. Definitions of Technical Terms, Degree of Obesity:

1. Obesity: BMI  $\geq$  30 to 40

2. Morbid Obesity: BMI  $\geq$  40 to 50

3. Super Morbid Obesity  $\geq$  50

##### B. Surgical Wound Classification: Definition of SSI is subdivided into three subsets.

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

- **Deep Incisional SSI** is 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 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](http://www.cdc.gov/ncidod/dhqp/pdf/guidelines/SSI.pdf)

#### CRITERIA FOR DEFINING A SURGICAL SITE INFECTION (SSI)

##### Superficial Incisional SSI:

- Infection occurs within 30 days after the operation &
- Infection involves only skin or subcutaneous tissue of the incision

and at least one of the following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision

is deliberately opened by surgeon, unless incision is culture-negative.

4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Do not report the following conditions as SSI:

1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).
2. Infection of an episiotomy or newborn circumcision site.
3. Infected burn wound.
4. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

### Deep Incisional SSI

- Infection occurs within 30 days after the operation if no implant is left in place or
- within 1 year if implant is in place & the infection appears related to the surgery and
- 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 (>38°C), localized pain, or tenderness, unless site is culture-negative.
  3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
  4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

#### Notes:

1. Report infection that involves both superficial and deep incision sites as deep incisional SSI.
2. Report an organ/space SSI that drains through the incision as a deep incisional SSI.

### Organ/Space SSI

- Infection occurs within 30 days after the operation if no implant is left in place or • within 1 year if implant is in place & infection appears related to the operation and
- infection 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.

### C. Formulation of TAAD Solution:

1. One-liter bag of physiologic 0.9% saline as solvent
2. Lidocaine 1gm and Epinephrine 1mg in 100ml
3. Sodium bicarbonate 10 mEq in 10ml
4. Cefazolin, 1gm of powdered cefazolin per bag of TAAD solution, dissolved in 10ml of saline obtained from the 1L bag of physiologic saline. Maximum dose of cefazolin by TAAD is 2gm.
5. Metronidazole, 500mg per bag of TAAD solution, where metronidazole is available as 500mg in 100ml and total TAAD dose not to exceed 1000mg.
6. Individual research sites may opt to routinely substitute one or more specified antibiotics for IV antibiotic delivery, instead of cefazolin and metronidazole, **but only with FDA and IRB clearance.**
7. Method of TAAD Solution Formulation (Preparation of the mixture of the TAAD solution):

- a. 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 and for 24 hours if refrigerated.
- b. 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.
- c. 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.
- d. 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.
- e. The TAAD solution should not be prepared without legible signed orders written by a physician, physician's assistant or nurse-practitioner.
- f. The components of each bag of TAAD solution (or a drug co-kit containing all the necessary ingredients for preparing a TAAD solution) will include the following items:

- 1 liter bag of 0.9% physiologic saline (sodium chloride)
- 1 gram of lidocaine and 1milligram of epinephrine in 100ml (two 50ml bottles) of 1% lidocaine and epinephrine 1:100,000, (or one 50 ml bottle of 2% lidocaine with epinephrine 1:50,000).
- 10 milliequivalents of sodium bicarbonate in 10ml of 8.4% sodium bicarbonate
- 1000mg vial of cefazolin powder
- 500mg of metronidazole in a 100ml bag of solution
- Either a sterile a 30ml syringe and an 18 gauge needle
- Two adhesive safety labels stating, **"Subcutaneous Tumescent Lidocaine, NOT for IV"**
- One label indicating the name of the patient, the name of the physician who wrote the order for the TAAD solution, the name of the person who prepared the bag of TAAD solution, a list of the drug contents of the bag, the date and time of preparation.

g. Each bag of TAAD solution should be prepared on a clean surface as follows:

1. Apply one safety label to each side of the 1 liter bag of saline

Using the syringe and hypodermic needle:

2. The maximum capacity of the IV bag may vary depending on the manufacturer. In order to accommodate the additional 210ml of fluid (lidocaine 100ml, metronidazole 100ml & Na Bicarb 10ml) that will be added to the 1000ml bag of saline when preparing the TAAD solution, it may be necessary remove some volume saline before injecting the lidocaine and metronidazole.
3. Transfer 100ml of 1% lidocaine with epinephrine 1:100,000 into the IV bag
4. Transfer 10ml of 8.4% sodium bicarbonate into the IV bag
5. Aspirate 10ml of solution from the IV bag into the 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.

6. 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.

7. Apply the label listing the names of the drugs and the name of the clinician to the bag of TAAD solution.

8. 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.

#### **D. Minimum Volume of TAAD Infiltration:**

The volume of TAAD solution to be used in this TAAD clinical trial is 1 bag to 2 bags. An average adult can easily be given at least 1 liter of TAAD solution. For this randomized clinical trial (RCT), the 1000ml is the minimal volume of TAAD solution for SSI prevention. The volume of TAAD solution to be used is a clinical decision to be made by the surgeon or anesthesiologist. A smaller volume can be infiltrated at the surgeon's discretion, especially in thin cancer patients who have little subcutaneous fat. If the volume of TAAD solution is too small, there may be no benefit to TAAD. Obese patients ought to be given 2 liters of TAAD solution. The total volume of TAAD solution and the formulation of the TAAD solution must be recorded. Insufficient volume of TAAD will exclude the subject from this RCT.

#### **E. Tumescent Lidocaine Anesthesia:**

Tumescent lidocaine local anesthesia is a method of regional local anesthesia. For the present research the maximum dosage of tumescent lidocaine will not exceed 28mg/kg, with or without general anesthesia (GA). A previous, WIRB-approved phase I clinical trial has established that the estimated risk of exceeding 6 mg of lidocaine per liter of serum at a dosage of 28mg/kg of lidocaine in a tumescent solution is less than 1 per 5,000,000 (**Klein JA, Jeske DR. Estimated Maximal Safe Dosages of Tumescent Lidocaine. Anesth Analg. 2016;122:1350-9**). The FDA has no scientific data relating to the recommended maximum safe dosage of lidocaine for infiltration local anesthesia (based on a Freedom of Information Act inquiry). TLA has been widely used since 1987 for tumescent liposuction. Guidelines published by the American Society of Plastic Surgery and the American Society for Dermatologic Surgery specify 35mg/kg to 55mg/kg for the recommended maximum safe dosage of tumescent lidocaine for liposuction.

#### **F. Method and Devices for TAAD Infiltration.**

**1. Tumescent Infiltration Cannulas:** HK Surgical tumescent infiltration catheters or cannulas will be used for infiltration of TAAD solution. Two types of tumescent infiltration cannulas are available: reusable stainless steel tumescent infiltration cannulas (HK Monty infiltration cannulas) or a single-use disposable sterile plastic catheter (HK SubQKath). No device will be used without FDA 510(k) clearance or investigative device exemption (IDE) approval.

**2. Tumescent Infiltration Pump:** Either an analog HK Surgical analog peristaltic infiltration pump (HK KIP II) or an HK Surgical digital infiltration pump (HK KTP). Both pumps have FDA 510(k) clearance.

**3. Disposable single-use sterile tumescent infiltration-pump tubing** supplied by HK Surgical.

#### **G. Approximate Number of Subjects**

Multicenter Center Trial: **approximately 330 to 660** (Group sequential analysis with one intermediate stopping point will be used) for a statistical power of 0.8.

#### **H. 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).

### I. 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. Safety of TAAD: Incidence of adverse events associated with

a) Dilute subcutaneous TAAD solution

b) Infiltration of TAAD solution

The following safety assessment check list will be completed between 24 to 36 hours after TAAD infiltration: Indicate (below) if any of the following tumescent-infiltration site signs and symptoms appear within the first 24 hours after surgery:

### TAAD ADVERSE EVENTS QUESTIONNAIRE

Problems: Check-Off One Answer per Problem	Grade 1 None	Grade 2 Mild/Moderate	Grade 3 Severe	Grade 4 Life-Threatening
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#### 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	Transfusions ≤ 2 units PRBC	> 2 units 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
Pancreatitis	None	Mild	Moderate	Severe or Life-Threatening

## 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

Altered Mental Status	None	Mild Lethargy, Somnolence	Confusion, Memory Impairment	Delirium, Obtundation, Coma
Ataxia	None	Detectable, Normal Activities	Moderate, Interfers with Normal Activities	Severe, Unable to do Self-Care
Headache	None	Mild, Doesn't Interfer with Activity	Moderate, Interfers with Activity	Severe, Unable to do Self-Care
Weakness Neuromuscular	None	Mild, Doesn't Interfer with Activity	Moderate, Interfers 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. RESPIRATORY

Acute Bronchospasm	None	Mild Symptoms, No treatment Requires	Moderate, Requires Treatment	Severe, Possibly Requires Intubation
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Dyspnea	None	Dyspnea on Exertion	Dyspnea at Rest	Respiratory Failure, Requires Intubation
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**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	≤ 38.6	38.6 - 39.3	39.4 - 39.9	≥ 40

**LABORATORY VALUES: (Compared to Baseline Prior to TAAD)**

ALT SGPT	Within Normal Limits or Borderline	NA	Significant Elevation	Severe Hepatitis
AST SGOT	Within Normal Limits or Borderline	NA	Significant Elevation	Severe Hepatitis
Amylase	Within Normal Limits or Borderline	NA	Significant Elevation	Life Threatening Pancreatitis

**HEMATOLOGIC**

WBC	Within Normal Limits or	NA	Severe Leukopenia	Life Threatening Leukopenia
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	Borderline				
Absolute Neutrophil Count	Within Normal Limits or Borderline	NA		Severe Leukopenia	Life Threatening Leukopenia
Platelet Count	Within Normal Limits or Borderline	NA		Severe Thrombocytopenia	Life Threatening Thrombocytopenia
AE Not Otherwise Specified					

3. Safety and efficacy of TLA solution
4. Safety and efficacy of subcutaneous infiltration catheter
5. Safety and efficacy of peristaltic tumescent infiltration pump for

#### J. 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.
4. Time from arrival in post-op recovery to time of ambulation).
5. Post-Op Narcotic Requirements (total mg and mg/kg)
6. Unexpected re-admission to hospital (for any reason)  $\leq$  30 days of surgery (Binary Data)
7. General Anesthesia Requirements (Quantitative Measure)
8. Diagnosis of Sepsis
9. Diagnosis of systemic inflammatory response syndrome (SIRS)
10. Diagnosis of C. Difficile colitis

#### K. 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 annual 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

**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 Oversight 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 Oversight 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 Tumescant Antibiotic Delivery plus Intravenous Antibiotic Delivery (TAAD+IVAD) versus IVAD alone.
- Because of the nature of tumescant 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.
- It is preferred that the another (different) clinician will do the clinical evaluations looking for surgical site infections (SSA).

**O. Statistical Analysis, Power Calculations and Samples Size Estimation**

Daniel Jeske PhD and Joyce Fu, 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 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 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]

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) Sequentially label 24 envelopes and 24 cards (5x7 inch) from 1 to 24.
- 2) Place each card inside the correspondingly numbered envelope.
- 3) Separate the envelopes-cards into groups of four each: {1,2,3,4}, {5,6,7,8},..., {21,22,23,24}.
- 4) Select a set of 4 envelopes, 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 envelopes.
- 7) Repeat this sequence until all 24 cards-envelops have been given a treatment assignment.
- 8) Arrange the envelopes 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 and 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.

#### **Q. Formulation and Dosage of TAAD Solution:**

TAAD can consist of cefazolin and metronidazole in a solution of tumescent lidocaine anesthesia (TLA). Each liter bag of TLA solution consists of lidocaine, epinephrine, sodium bicarbonate added to a 1 liter bag of 0.9% saline or lactated Ringer's solution or Hartman's solution.

Each bag of TAAD solution will contain:

**Cefazolin** 1gm as desiccated powder dissolved in saline from the bag 0.9% saline or a balanced salt solution.

**Metronidazole** 500mg/100ml

**Lidocaine** 1000mg & Epinephrine 1mg in 100ml of lidocaine (1%) with epinephrine (1;100,000)

**Sodium Bicarbonate** 10mEq in 10ml of sodium bicarbonate (8.4%)

**Physiologic Saline** 0.9% 1000ml

Total volume = 1210ml

#### **R. TAAD Dosages & Delivery:**

**With general anesthesia**, in patients who do not have significant cardiac, hepatic or renal impairment, the maximum lidocaine mg/kg dosage will not exceed 28 mg/kg, which, in a 70kg patient, is approximately 2gm of lidocaine in 2 bags of TAAD solution. Patients who do have significant cardiac, hepatic or renal impairment are excluded from participating in this TAAD RCT.

**Without out general anesthesia**, the maximum lidocaine mg/kg dosage will not exceed 28 mg/kg, which, in a 70kg patient, is approximately 2gm of lidocaine in 2 bags of TAAD solution.

The total volume of TAAD solution will probably range from 1210ml in small patients and up to 2420ml in obese patients; in other words, approximately 1 to 2 bags of TAAD solution. The minimum volume of TAAD solution (in very thin patients) is 500ml. The determination of the actual volume of TAAD solution to be infiltrated is made by the surgeon or anesthesiologist. The initial studies will allow a more precise estimate of the range of volumes. The targeted area of subcutaneous tissue to be infiltrated with TAAD solution should 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. For the abdomen, the total width of subcutaneous tumescence (the ambit of TAAD infiltration) will be about 20 to 40 cm.

Total TAAD antibiotic mg dosages will conform to community standards of care, which may exceed antiquated package insert labeling. Recent publications have shown that in certain clinical situations (e.g. obesity) the bioavailability, peak concentration (Cmax) and Time Above MIC (T>MIC) of antibiotics in subcutaneous tissue are sub-therapeutic. Thus, recent peer-reviewed evidence based mg dose recommendations typically exceed cefazolin product labeling.

Delivery of TAAD solution by subcutaneous infiltration will be accomplished using HK Surgical peristaltic infiltration pump, peristaltic infiltration tubing, and SubQKaths (disposable, single use, subcutaneous infiltration cannulas). All devices will have FDA 510(k) clearance or FDA investigative device exemption (IDE).

**Instructions for Preparing TAAD Solution** will be included in the research manual.

**Instructions for Tumescence Infiltration** will be included in the research manual.

#### **S. Research Design: Drug Delivery Timing and Technique**

- IVAD timing: For IVAD alone (without TAAD) the IVAD infusion should 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: infiltration to be completed less than 4 hours prior to skin incision. For IVAD + TAAD, the IVAD will be initiated and completed before the incision. The actual time from start to completion of IVAD will be recorded.
- Subcutaneous infiltration will be accomplished by using HK tumescent infiltration cannulas and HK peristaltic tumescent infiltration pump and infiltration pump tubing. All devices will have FDA clearance/approval. Infiltration procedure will be carried out with either the patient awake with minimal or no sedation or with IV or IM sedation or while the patient is under general anesthesia. The patient and surgeon will determine which of these infiltration options will be used.

#### **T. Criteria for Diagnosis of SSI, VTE & Sepsis**

**Criteria for Diagnosis of SSI** will be defined according to the criteria of the Centers for Disease Control updated and published August 2011<sup>53</sup>. Admittedly the CDC definition is complex and requires some training for effective use. See section iv B above, or equivalently [www.cdc.gov/nhsn/pdfs/pscmanual/9pscscsscurrent.pdf](http://www.cdc.gov/nhsn/pdfs/pscmanual/9pscscsscurrent.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.

**Criteria and Methods for Diagnosis of VTE** to be determined and standardized by each research site.

**Criteria and Methods for Diagnosis of Sepsis** to be determined and standardized by each research site.

#### **U. Methods to Reduce Potential for Bias in Outcome Determination:**

There will be two separate types of questionnaires.

**SSI, VTE, Sepsis 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.

**Mode of Delivery Side Effects Questionnaire:** There will be two questionnaires regarding possible side effects of tumescent antibiotic delivery (TAAD). One questionnaire will be concerned with possible acute local tissue toxicity and acute systemic toxicity, which will be administered 18 to 36 hours after surgery. The second questionnaire will be a “discharge questionnaire” to be completed on the day of discharge from the hospital or clinic.

Different persons will be assigned to administer the two different questionnaires. The persons who administer will be “**SSI, VTE, Sepsis**” questionnaires will be instructed to not discuss their results with the persons who administer the “**Side Effects**” questionnaire.

#### **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 after discharge 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 palpitations, 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.

**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 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.

### **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. These drugs have been used for TAAD in the previous WIRB-approved research. See the following peer-reviewed publications of 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 that clinical trial.

**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 generic drug with a well-established safety profile. These include Lidocaine, Epinephrine, Sodium Bicarbonate, and physiologic 0.9% saline. These drugs have been used for TLA in the previous WIRB-approved and now closed protocol (WIRB® Protocol #20050127) entitled: Bioavailability and Absorption Kinetics of Tumescent Lidocaine (clinicaltrials.gov NCT00977028). That research project estimated that, for a TLA lidocaine dosage of 28mg/kg without liposuction and without general anesthesia, the risk of mild lidocaine toxicity (serum lidocaine concentration  $\geq 6\mu\text{g/ml}$ ) is 1 per 5,000,000. In the present clinical trial the maximum dosage of tumescent lidocaine will be 28mg/kg without general anesthesia and 21mg/kg with general anesthesia.

**4. Safety of Tumescent Infiltration Technique and Devices:** The technique for tumescent infiltration is 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 maximum dosage of tumescent epinephrine to be used in this clinical trial is not expected to produce any clinical problems associated with tachycardia.

**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:

**1) 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.

#### 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 palpitations, 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.

**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.

Criteria for diagnosis of surgical site infection (SSI) & Protocol guidelines in performing the primary assessment of SSI:

- During hospitalization, daily visual & physical exam of incision site will be done.
- Between post-op days 30 to 45, patient is to be evaluated and/or interviewed and/or patient's chart will be reviewed.

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