VANCO:
Statistical Analysis Plan for Main Outcome Paper
(Revision 2)

NCT02227446

February 4, 2020

Revision 2 Information:

- Section 5, "nd" changed to "and"
- Section 8.2: "surgery during the index hospitalization" changed to "definitive fixation surgery"

Revision 1 (9/7/18) Information:

- Section 8.1: "The primary way in which the presence or absence of the occurrence of clinical outcome events are ascertained is through study follow-up visits. Presence/absence of events are also ascertained via medical record reviews where there is documented orthopaedic contact." changed to "The primary way in which clinical outcome events are ascertained is through study follow-up visits. Presence/absence of infection events are also ascertained via medical record reviews where there is documented orthopaedic contact."
- Section 8.3: "Key secondary outcomes include: (1) superficial surgical site infection, (2) loss of limb/amputation, (3) fixation failure, (4) wound dehiscence, (5) wound seratoma/hematoma and (6) surgical site infection at other surgical site. If multiple events for a given secondary outcome occur for an individual, only the timing of the first event will be considered. Treatment effects will be analyzed using the same approach described for the primary outcome." changed to "Key secondary outcomes include: (1) superficial surgical site infection, (2) loss of limb/amputation, (3) fixation failure, (4) wound dehiscence and (5) wound seratoma/hematoma. If multiple events for a given

secondary outcome occur for an individual, only the first event will be considered. For superficial surgical site infection, treatment effects will be analyzed using the same approach described for the primary outcome. To the extent possible, treatments effects for other secondary outcomes will be analyzed using the window-based method."

- Section 8.4: "Treatment effects will be analyzed using the same approach described for the primary outcome." changed to "To the extent possible, treatments effects for these outcomes will be analyzed using the window-based method."

The statistical analysis plan was finalized prior to database lock. Prior to database lock, the only analyses that were performed were (1) those masked to treatment group for purposes of DSMB reporting, (2) evaluation of background rates (to assess design assumptions) in August 2016, and (3) a formal DSMB interim analysis of the primary outcome conducted in November 2016.

1 CONSORT Diagram

The CONSORT Diagram will report the following items in sequential order: (1) the number screened patients, (2) the number of patients not enrolled and associated reasons, (3) the number of enrolled and randomized patients, (4) number randomized to treatment group, number randomized to control group, (5) within treatment group, the number of late ineligibles and late refusals and whether they received treatment, (6) within treatment group, number of cross-overs, (7) within treatment group, number included in survival analysis- and window-based analyses with summary statistics related to missing/censored data. Late ineligibles and late refusals will be removed from all analyses. The outcomes, complications, adverse events of late ineligibles and late refusals who received treatment will be reported.

2 Follow-up Time

Patients were expected to return for study follow-up visits at 2 weeks, 3 months and 6 months. In addition, medical record reviews were conducted to determine whether there was documented orthopaedic contact beyond the last study follow-up visit. The end of follow up will be defined as the last study follow-up visit or the last orthopaedic contact if applicable, and follow-up time will be the duration between the last fixation procedure and

the end of follow up. A figure showing the distribution of follow-up time by treatment group will be produced. Differences between treatment groups will be evaluated by using Wilcoxon rank-sum test. Details of reasons for premature study discontinuation will be presented.

3 Pre-Injury Characteristics

A table will report summary statistics for characteristics of participants prior to their injuries by treatment groups. Pre-injury characteristics include age, gender, education, body mass index, tobacco use, alcohol abuse, drug abuse, diabetes, poverty status[1], previous injury to study leg, pre-injury infection and associated treatment and pre-injury VR-12 (general health, physical component score, mental component score).

4 Injury Characteristics

A table will report summary statistics for injury characteristics by treatment groups. Injury characteristics include bone segment (tibia plateau/tibia pilon), fracture pattern per the AO/OTA classification (B/C), open fracture (yes/no), Tscherne classification (among closed fractures), Gustilo type (among open fractures), OTA Open Fracture Classification (including contamination, bone loss, muscle damage, skin damage, and arterial damage) and severity of injuries other than study injury (as measured by AIS).

5 Pre-, Intra-, and Post- Operative Care Characteristics

A table will report summary statistics for pre-, intra- and post-operative care characteristics by treatment groups. These characteristics will include pre-operative risk stratification (ASA, nasal swabs[2]), nutrition lab results, prophylactic antibiotic use (prior to skin incision), other antibiotic use (24 hours prior to definitive fixation), number of stages prior to final fixation, days to definitive surgery (relative to injury), number and location of surgical incisions (stratified by fracture type), percutaneous insertion (yes/no), surgical site skin preparation, nasal application of Bactoban (yes/no), external

[1]Derived variable based on self-reported income and household size; anticipated to have high rate of missingness.

[2]MRSA swab is preoperative (prior to incision). MRSA positive is assumed to be risk for infection.

fixation removed during surgery (yes/no, if applicable), fraction of inspired oxygen (FiO_2) during the surgery (yes/no), number of other procedures, duration of surgery, use of tourniquet, operative environment, attending surgeon time in surgery (as percent of total surgery time), type of anesthesia, additional novel (per surgeon self report) techniques to reduce risk of infection (yes/no), use of a surgical drain (yes/no), incisional vac (negative pressure wound therapy, or NPWT) at surgical site (yes/no), planned time to allow range of motion, and peri-operative antibiotic treatment.

6 Adherence to Treatment Protocol and Protocol Deviations

Patients randomized to the treatment arm should receive only one dose of local Vancomycin, consisting of 1 gram of powder. The study treatment should only be administered at the final stage of fixation if the procedure is done in multiple stages. Patients randomized to the control arm should not receive any local Vancomycin powder as part of their definitive fixation. Lack of adherence to the assigned treatment will be reported as protocol deviations, the details of which will be reported by treatment group. Among patients who received local Vancomycin powder, including those that crossed over from the control arm, the method of application and severe allergic reaction to local Vancomycin powder (yes/no) will be reported.

7 Serious Adverse Events and Complications Other than Outcomes

A table will report a summary of deaths, life-threatening or disabling events, and complications other than outcomes, stratified by treatment group.

8 Outcome Analyses

8.1 Ascertainment

The primary way in which clinical outcome events are ascertained is through study follow-up visits. Presence/absence of infection events are also ascertained via medical record reviews where there is documented orthopaedic contact.

8.2 Primary Outcome

The primary outcome is the presence of clinically significant deep infection (as determined by adjudicators applying CDC guidelines)[3] by 6 months after the last definitive fixation surgery. There are two ways that the results will be reported: (1) time-to-event-based, and (2) window-based.

The first method is based on survival analysis techniques.[4] Specifically, Kaplan-Meier (KM) methods will be used to estimate, separately for each treatment group, the probability of a deep infection by 182 days. Additionally, 95% confidence intervals for the difference and ratio of treatment-specific probabilities of deep infection by 182 days will be computed. Kaplan-Meier curves for both treatment groups will be produced.

The second method is based on the creation of a 42-day (i.e. six week) window around day 182.[5] A patient is said to have a deep infection if, had they been assessed within the window, they would have been recorded to have experienced a deep infection prior to the assessment time. This binary outcome will be counted for patients who were observed to have an infection prior to day 140 AND all patients whose end of follow-up was after day 140. That is, the outcome will be unobserved for those whose end of follow-up is prior to day 140 AND did not experience a deep infection during follow-up.[6] The treatment-specific probability of deep infection will be estimated by using the observed outcomes. 95% confidence intervals for the difference and ratio of treatment-specific probabilities of deep infection will be computed. A test of treatment difference will be evaluated using Fisher's exact test.

Sensitivity analyses will be conducted to evaluate the robustness of results. Examples include altering the permissible follow up window width, using last study follow-up visit as the end of follow-up (rather than including last orthopaedic contact), and addressing informative missingness/censoring by adjusting for key baseline covariates predictive of infection (e.g., fracture type, ASA grade).

For all deep infections, the ASEPSIS score will be summarized by treatment group.

[3] Details of the adjudication process and its findings will be reported.

[4] This method was used for the interim analysis, when ascertainment was not complete.

[5] This is consistent with what was proposed in the protocol paper.

[6] It was assumed that the fraction of patients with unobserved data would be less than 5%. During the blinded ascertainment process, it became clear that the fraction would be larger than 5%. As a result, the first method may make more efficient use of the observed data.

8.3 Secondary Outcomes

Key secondary outcomes include: (1) superficial surgical site infection, (2) loss of limb/amputation, (3) fixation failure, (4) wound dehiscence and (5) wound seratoma/hematoma. If multiple events for a given secondary outcome occur for an individual, only the first event will be considered. For superficial surgical site infection, treatment effects will be analyzed using the same approach described for the primary outcome. To the extent possible, treatments effects for other secondary outcomes will be analyzed using the window-based method.

8.4 Tertiary Outcomes

Key tertiary outcomes include: (1) nonunion, (2) malunion, (3) flap failure, (4) peri-implant fracture, (5) reaction to hardware. If multiple events for a given tertiary outcome occur for an individual, only the first event will be considered. To the extent possible, treatments effects for these outcomes will be analyzed using the window-based method.

9 Subgroup Analyses

Two key subgroup analyses will be conducted with regards to the primary outcome: plateau/pilon and open/closed. An interaction test will be performed to evaluate if there is statistical evidence of differential subgroup effects within subgroup categories. Treatment effects within subgroups will be reported using the same approach described for the primary outcome.

Daniel Scharfstein

Digitally signed by Daniel Scharfstein
Date: 2020.02.04 20:22:06 -05'00'

Prepared by:
Daniel O. Scharfstein (ScD), Principal Biostatistician
Yanjie Huang (BM, ScM), Data Analyst

Approved by:
Robert V. O' Toole (MD, MSME), Principal Investigator
Renan C. Castillo (PhD), MCC Investigator
Anthony R. Carlini (MS), Project Director