Statistical analysis plan

**Objectives**

In this study, we aim to examine the relative effects on the perioperative treatment with 6 specific antithrombotic drugs on the incidence of prosthetic joint infections (PJIs) after prosthesis surgery. Previous studies have provided heterogenous results, and there is clinical equipoise regarding the optimal choice of thromboprophylaxis. We will also estimate 90 day baseline cumulative incidence of PJI in Mexican patients not having received chemical thromboprophylaxis in four different surgical population: patients receiving hip, knee, ankle and shoulder prostheses.

**Data source**

We will analyze data sets from the Prosthesis Surgery Registry in Mexico. All patients with available data in from registry inception until the current date will be analyzed.

**Subgroup analyses**

For baseline 90-day cumulative incidences of PJI for each surgical population (hip, knee, shoulder and ankle) without chemical thromboprophylaxis, a subset of the data corresponding to the relevant population will be generated. For the relative effects of different antithrombotic drugs on the cumulative incidence of PJI, estimates will be calculated based on the entire data set.

**Endpoints**

The primary outcome will be whether a prosthesis infection has developed before the 90th postoperative day. We assume no infections directly related to the surgical procedure will arise after this. The primary endpoint will be generated from registry data as a dichotomous variable (*prost\_inf*)

**Exposures and covariates**

The following covariates will be generated from registry data:

1. Age at surgery (*age* - integer)
2. Location of surgery (*surg\_location* – factor variable [HIP, KNEE, SHOULDER, ANKLE])
3. Gender (*gender* - dichotomous)
4. Health institution performing surgery (*hosp\_surg* – factor variable)
5. Geographical location (state) of health institution within Mexico (*state\_hosp* – factor variable)
6. Basic preoperative physical measurements on day of admission:
   1. Systolic blood pressure (*bt\_syst* - integer)
   2. Heart rate (*hr* - integer)
   3. Temperature (*temp* – floating point)
7. Pooled Charlson comorbidity index scores across all domains (*charlson* – integer)
8. Type of prosthesis (*prosth\_type* – factor variable)
9. Use of perioperative medical thromboprophylaxis. Prescription of a 10-day course or longer of a specific drug will be coded as a dichotomous variable. The following drugs will be assessed:
   1. Aspirin (*asa*)
   2. Low molecular weight heparin (*lmwh*)
   3. Rivaroxaban (*rivarox*)
   4. Apixaban (*apix*)
   5. Dabigatran (*dabig*)
   6. Edoxaban (*edox*)
10. Use of perioperative mechanical thromboprophylaxis (*mech\_prophyl* – dichotomous)
11. Use of perioperative antibiotic prophylaxis – (*antib\_prophyl* – dichotomous)
12. Duration of surgery in minutes (*dur\_surg* - integer)
13. Patient mobilization status on first postoperative day (*mobil\_day\_1* – dichotomous - mobilized: yes/no)
14. Smoking status (*smoker* - dichotomous)

**Statistical procedures**

For obtaining a crude estimate of the 90-day cumulative incidence, we will compute proportions of patients within each surgical population (hip, knee, shoulder, ankle) having developed a PJI by the 90th postoperative day, with Agresti-Coult confidence intervals.

We will compute odds ratios (ORs) for developing PJI with each antithrombotic drug by fitting a mixed-effects logistic regression model. We will use a nested random effects model with a random intercept for *hosp\_surg*, nested within *state\_hosp*. We will also fit a random intercept for *state\_hosp*. We will fit the following maximal model:

where represents the index of the geographical area (*state\_hosp*), the index of the hospital within the geographical area (*hosp\_surg*), and the index of the observation within the hospital.

We will assess model fit with Q-Q plots and residual plots. We will attempt model reduction by successively removing variables *bt\_syst*, *hr*, *temp*, *mobil\_day\_1* and assess the reduced models using Akaike’s Information Criterion (AIC). A more parsimonious model providing a good fit will be preferred. For testing the hypothesis that ORs of PJI are different between exposure groups, we will perform a Tukey post-hoc test with a Bonferroni-Holm correction.

**Software**

All analyses will be performed in R version 3.4.31. For the mixed-effects analysis, we will use the lmer and AIC functions from the lme4 package2, as well as the lmerTest package3 for presenting results. For Tukey post-hoc tests, we will use the glht function from the multcomp package4, with parameters linfct = mcp(Group = “Tukey”) and test = adjusted(“holm”).

1. 1. R: A language and environment for statistical computing [program]. Vienna: R Foundation for Statistical Computing, 2017.
2. 2. Bates D, Mächler M, Bolker B, et al. Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software* 2015;67(1):1-48. doi: 10.18637/jss.v067.i01
3. 3. Kuznetsova A, Brockhoff P, Christensen R. lmerTest Package: Tests in Linear Mixed Effects Models. *Journal of Statistical Software* 2017;82(13):1-26. doi: 10.18637/jss.v082.i13
4. 4. Hothorn T, Bretz F, Westfall P. Simultaneous Inference in General Parametric Models. *Biometrical Journal* 2008;50(3):346-63.