Study Title
A Retrospective Study to Understand the Risk Factors/Drivers of Inappropriate" Antimicrobial Use and the Performance Evaluation of a Clinical Decision Support Tool that Facilitates Prediction of Outbreaks of Inappropriate Antibiotic Use

Objective 1. The first objective of this study is to comprehensively classify and predict vancomycin never-events.

Vancomycin is selected as a prototypical broad-spectrum antibiotic that is regularly overused and is known to cause downstream harms (e.g., acute kidney injury). We will classify the proportion of vancomycin use in which potential for harm outweighs the potential benefit, herein referred to as "never events". We will categorize the rate of never events as a function of patient, provider, and disease/organism characteristics.

Objective 2. We will develop decision rules and thresholds (e.g. *decision support tools*) to predict time periods with frequent vancomycin never events based on antimicrobial consumption trends.

Objective 2a. Identify the relationship between clusters of high antibiotic use, herein referred to as "outbreaks," and occurrence of never events. We will use our previously published strategies to identify antibiotic outbreaks and correlate to vancomycin never events.

Objective 2b. Compare thresholds for prediction of never events based on Optimal Data Analysis (ODA) methodologies with exact statistics versus vancomycin never events.

STATISTICAL METHODS
For Objective 1, multivariate logit models will be created using never events as the dependent variable and the hospital, provider and patient covariates listed above as the independent variables. Models will be built using forward stepwise procedures ($P<0.2$) for model inclusion and $P<0.1$ for retention. The final model selection will utilize Akaike Information Criteria scores to ensure the most informative and parsimonious model.

For Objective 2a, multivariate linear models of vancomycin use will be completed using segmented regressions stratified by each individual site (i.e. Northwestern, Henry Ford Hospital, University of Michigan). Predictive intervals for antibiotic use will be calculated. *Antibiotic Outbreak' months* will be defined as the antibiotic use level that best predicts the highest quartile of vancomycin never events. That is, we will optimize sensitivity and specificity for prediction of never events using binary recursive partitioning methods (to identify optimal categorical classifications) we have previously established. We will attempt to combine data from all three sites using multilevel mixed-effects models. If this is not possible, we will analyze each site individually. Performance (e.g. sensitivity, specificity, etc.) of the prediction for antibiotic outbreaks will be compared to the occurrence of vancomycin never events.

Statistical analyses conducted in O2b are theoretically similar but mathematically distinct. The methods in O2b address maximum-accuracy calibration, sensitivity, and prospective cross-generalizability analysis of models identified in O1 and O2a. O2b analyses will use a machine-learning algorithm that is known as optimal (i.e., maximum-accuracy) discriminant analysis, or ODA. To identify and mitigate over-fitting, prospective cross-generalizability of optimized models is assessed using one-sample ("leave-one-out") jackknife analysis.