A Trial of Automated Outbreak Detection to Reduce Hospital Pathogen Spread

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CLUSTER Project
Full Statistical Analysis Plan

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Background

The CLUSTER (**C**luster **L**inkage **U**sing **S**tatistics to **T**rigger and **E**valuate **R**esponse) Trial is a cluster-randomized trial in 82 HCA Healthcare (HCA) affiliated hospitals designed to assess a statistically-based automated method for detecting clusters of hospital acquired infections, compared to routine assessment. The CLUSTER Trial will assess the impact of a space-time statistical software tool, WHONET-SaTScan, on guiding response and containment of hospital-based clusters.

Hospitals have been randomized to:

- **Arm 1**–Routine cluster detection coupled with an evidence-based cluster response protocol
- **Arm 2**–Enhanced cluster detection using an automated cluster detection tool and routine cluster detection, coupled with an evidence-based cluster response protocol

Trial Outcomes

Clusters will be identified based upon WHONET-SaTScan analyses occurring in real time, in both intervention hospitals and in routine surveillance hospitals. The primary outcome is cluster size: the number of cluster cases identified after the initial cluster signal from the WHONET-SaTScan software. The secondary outcome is the cluster duration: the number of days from the initial cluster signal through the last cluster case. WHONET-SaTScan identifies the beginning of a cluster using a p-value threshold, and we define the end of a cluster as the date of the last case meeting the p-value threshold, by the close of the 180 day window, or end of the trial, whichever date is earlier.

Trial outcomes are found in the below table.

Outcome	Metric
Primary Trial Outcome	
Cluster size	Number of cases identified after the initial cluster signal through the last cluster case
Secondary Trial Outcome	
Cluster duration	Number of days from the initial cluster signal through the last cluster case
Pre-specified secondary exploratory analyses (secondary manuscript)	
Genetic relatedness of clusters	Compare the genetic relatedness of isolates within a cluster, defined by the automated cluster detection tool or routine cluster detection methods

Analysis

Our primary analysis will be an unadjusted generalized linear mixed model that assumes a negative binomial distribution and accounts for groupings of clusters within each hospital. Model terms will include arm (intervention or routine surveillance group), trial period (baseline vs. intervention) and an interaction term between trial period and arm. The assessment of trial success in decreasing the size of clusters will be determined by the significance of the interaction term, which assesses whether the difference in cluster size between the baseline and intervention period differs significantly between the two arms. This model will be used for both the primary and the secondary outcome.

We can write this model symbolically as:

$$\log(y_{ij}) = \beta_0 + \beta_1 Arm_{ij} + \beta_2 Period_{ij} + \beta_3 Arm_{ij} * Period_{ij} + b_{0i} + b_{1i} * Period_i$$

where i is a hospital, j is a signal within the hospital, Arm and $Period$ are indicator variables and are = 0 for signals in a hospital in the routine surveillance arm or baseline period and 1 if in the intervention arm or period. The b_{0i} and b_{1i} are random effects, and account for the clustering within a given hospital, equivalent to usual length or size of cluster at each hospital. These may differ in the baseline and intervention periods. The ultimate effect of the intervention is assessed through β_3: as parameterized, if it is negative and has p-value < .05 (or 95% CI excluding 0) then the intervention reduces the size (primary outcome) or duration (secondary outcome) of clusters.

Subsequent analyses will include as-treated and adjusted models. As treated models in this setting correspond to coding hospitals according to whether they actually implemented the WHONET-SaTScan system. All analyses will be performed using current versions of SAS (9.3, as of writing, SAS Institute, Cary NC) and/or R (3.6.1, as of writing).[1] These analyses will not be included in formal multiple comparisons adjustment because these are non-independent assessments related to the as-randomized unadjusted analyses. Results will be reported only as estimated effects and confidence limits, in keeping with current recommendations.[2] Types of clusters based on pathogen type will be provided as descriptive tables without including statistical analysis.

In a secondary paper, we will describe the genetic relatedness among isolates involved in the clusters that are available for whole genome sequencing. Using distance metrics, such as single nucleotide polymorphism-based genetic distance, we will identify those clusters of isolates that are consistent with outbreaks, and compare those clusters identified by WHONET-SaTScan and routine detection methods. Where available, background stains will be used to help define the baseline diversity and to contribute to estimates of the genetic relatedness among isolates involved in clusters.

Power Assessment

In many settings, an analytic approach to power is possible given that the assumptions of the model (e.g., logistic regression) are met and a relatively simple solution exists. However, generating the expected values to plug in may be difficult. In addition, some settings are complex enough that closed-form solutions may be difficult to generate. Many cluster-randomized designs fall into this class. In cluster-randomized studies, it is

also difficult to obtain reliable estimates of the additional parameters that are required, most notably the between-cluster variance or, equivalently, the intra-class correlation coefficient.

We assessed power using a custom-built simulation/resampling approach. This allowed us to incorporate detailed information from data collected from the hospitals in the study. Briefly, to calculate power by simulation, we 1) generated data under the alternative hypothesis-the data we anticipated seeing; 2) fit the model we planned to fit in the actual study; and 3) recorded whether we rejected the null hypothesis of no detectable effect in the simulated data. We repeated this process many times, and the proportion times we rejected the null hypothesis was used as an estimate of the power under the alternative hypothesis which we used to simulate the data.

Our simulation is based on the actual arm assignments for the trial. For the simulated baseline period in each arm, we use the observed clusters, rather than simulating new clusters; we assume that all clusters are as observed, with a probability of additional cases or days in each arm. In the simulated intervention period, the routine surveillance arm has the observed number of cases from the observed data, while the intervention arm has the effect described below.

We assumed that the intervention would have no effect in 20% of the intervention hospitals. Using the clusters observed in the baseline period within each hospital, we assumed that we prevent 30-50% of the cases after an initial signal during the intervention period in the intervention hospitals, with the actual reduction chosen by a uniform distribution over the described range on a per-outbreak basis. We also assumed that we would shorten the clusters by 50-70% of the observed length after an initial signal in the intervention period in the intervention hospitals. In addition, the extra days and cases added probabilistically to each cluster in the baseline period are not added in the intervention period. Thus, the simulation assumes a secular effect of smaller and shorter clusters.

We then fit the model described above. For our primary analysis, we achieved a power of 100% (95% CI 99.6%,100%) for the main (size) outcome and power of 79% (95% CI 77%, 82%) for the secondary duration outcome. Other assumptions reflected in this estimate include an alpha error level of 0.05.

References:

1. R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

2. Harrington D, D'Agostino RB, Gatsonis C, et al. New Guidelines for Statistical Reporting in the Journal. NEJM. 2019;381:285-6.