

Statistical Analysis Plan for “Quantitative evaluation of the effects of the 2013 New York State sepsis Regulations”

Version Note: This PDF is identical to the Open Science Foundation project registration submitted on June 18, 2018, with the only exception being the inclusion of the graphical equations.

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I. OVERVIEW

This registration provides an overview of our planned evaluation of the 2013 New York State sepsis regulations, colloquially known as “Rory’s Regulations”. This analysis plan is submitted for registration on June 18, 2018. We set the methodological decisions contained herein prior to receiving the full data set in order to facilitate transparent reporting of the study results and limit any biases that might occur through iterative post-hoc analyses. This project is funded by a research grant from the United States Agency for Healthcare Research and Quality (R01HS025146; PI: Kahn).

II. BACKGROUND AND GOAL

Sepsis is a leading cause of morbidity and mortality in the United States (1), yet a large proportion of sepsis patients fail to receive evidence-based care (2). To address this problem, policy makers are increasingly turning to regulatory mechanisms designed to mandate sepsis performance improvement in the form of care protocols for early recognition and treatment (3). A pioneering example of these mandates are regulations adopted by the New York State Department of Health in May 2013, called “Rory’s Regulations” in honor of the late Rory Staunton (4). These regulations require all acute care hospitals in the state to develop and implement protocols for timely sepsis treatment. The overall goal of the present evaluation is to determine the impact of these regulations on clinical outcomes and resource utilization. We will utilize a difference-in-difference approach, comparing temporal trends in New York State to trends in selected control states.

III. STUDY DESIGN

We will perform a retrospective cohort study of adult patients hospitalized with sepsis in adult general short stay acute care hospitals from 2011 to 2015. We will examine sepsis outcomes before and after implementation of the sepsis regulations in New York State, comparing these changes to those in control states that did not adopt sepsis regulations during this time. We will use four control states: Florida, Massachusetts, Maryland, and New Jersey. These control states were chosen because they have similar demographic characteristics to New York and, except for Florida, they are geographically proximal to New York. We will consider Pennsylvania as an additional control state pending data availability.

IV. STUDY HYPOTHESES

Our primary hypothesis is that patients in New York State, when compared to patients in control states, experienced improved sepsis-related outcomes after the implementation of Rory’s Regulations.

V. DATA SOURCES

Patient level data from New York, Florida, Massachusetts, Maryland, and New Jersey will be obtained from the United States Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project. Hospital level data will be obtained from the Healthcare Cost Report Information System (HCRIS), which is publicly available from the Centers for Medicare and Medicaid Services (CMS); and the American Hospital Association (AHA) Annual Survey. We will link the hospital level datasets to the patient level datasets using the hospital identifier from the AHA Annual Survey and the CMS provider number in HCRIS.

VI. HOSPITALS

We will exclude hospitals that we are unable to link to the HCRIS or AHA datasets due to missing, incomplete, or inaccurate hospital identifiers; as well as hospitals for which key variables in the HCRIS and AHA datasets are missing. We will further limit our analysis to adult general short stay acute care hospitals. Additionally, to help create a homogenous sample of hospitals across states, we will categorize hospitals based on the following characteristics: bed sizes of <100, 100 to 250, or >250; academic statuses of non-teaching (resident full-time-equivalent to bed size ratio of 0), small teaching (resident full-time-equivalent to bed size ratio between 0 and 0.2), or large teaching (resident full-time-equivalent to bed size ratio of 0.2 or higher); and regional populations of small (non-metropolitan statistical area or metropolitan statistical area population <100,000), medium (metropolitan statistical area population 100,000 to 1 million), or large (metropolitan statistical area population >1 million). With three characteristics and three categories for each characteristic, there are a total of $3 \times 3 \times 3 = 27$ possible characteristic combination groups. We will exclude hospitals in groups that appear only in the control states or only in New York State in either the pre-intervention period or in the post-intervention period.

VII. PATIENTS

In the primary analysis we will identify sepsis based on either a) the presence both infection and organ failure in the manner of Dombrovskiy, which we refer to as "implicit" diagnosis of sepsis (5); or b) an "explicit" diagnosis of severe sepsis or septic shock, with or without a concurrent organ failure. The implicit and explicit diagnoses are based on previously published International Classification of Diseases—version 9.0—clinical modification (ICD-9-CM) codes (1). Using both implicit and explicit diagnoses is less specific but more sensitive than approaches which rely exclusively on the explicit diagnosis of severe sepsis or septic shock and captures a larger patient population than is identified by clinical screening (6). In choosing a broad sepsis identification strategy rather than a narrower strategy, we sought to account for the fact that many patients with sepsis may be missed by clinical screening yet are still eligible for evidence-based care (7). All adult patients with sepsis will be eligible for the primary analysis. We will exclude patients with missing values for key covariates.

VIII. OUTCOMES

Our primary outcome variable will be in-hospital mortality by day 30 of hospitalization. We will also consider four secondary outcomes: ICU admission rates, central venous catheter insertion rates, Clostridium Difficile infection rates, and hospital length of stay. We will define these variables using elements available in the administrative records. Specifically, we will define in-hospital mortality using discharge status; hospital ICU admission using revenue codes; central venous catheter insertion and

Clostridium Difficile infection rates using validated ICD-9-CM codes; and hospital length of stay using directly reported values.

IX. COVARIATES

Patient level variables for case-mix adjustment will include age, gender, race, emergency department utilization, transfer from an acute care hospital, organ failures present on admission in the manner of Elias (8), sepsis infection categories in the manner of Ames (9), co-morbidities defined in the manner of Elixhauser (10). We will exclude sepsis infection categories if there is not sufficient variation across the sample. To prevent bias by variation in coding patterns across states, we will retain a maximum of 25 diagnosis codes and 15 procedure codes in each state and year. Hospital-level variables for case-mix adjustment will include categorical variables for hospital size using number of beds, hospital academic status using resident-to-bed ratio, and geographical region population.

X. PRIMARY ANALYSIS

Our primary approach will be a difference-in-difference (DiD) analysis to test the relationship between the New York State sepsis policy and outcomes. We will perform the analysis separately for each outcome variable described above. For all hypothesis tests we will consider a p-value of ≤ 0.05 to be statistically significant.

In the simplest DiD specification, the independent variables of main interest are a treatment indicator (here, New York State versus controls) and an indicator for pre-intervention versus post-intervention period. The interaction of these two variables is included and the point estimate for the interaction term is the estimated impact of the intervention in the full post-intervention period. One drawback of this approach is that it does not allow for the intervention effect to change over time. A second drawback is that it forces potentially arbitrary choices about the exact start date of an intervention, whether or not to include a phase-in period, and, if so, the length of the phase-in period. These choices will necessarily affect the final estimates of the policy effect.

Several factors make these issues particularly salient in our analyses. First, the introduction and implementation of Rory's Regulations was staged, spanning several years. On April 1, 2012, Rory Staunton died from sepsis leading to media coverage in the New York Times in the summer of 2012. By January 2013, New York State Governor Andrew Cuomo announced that Rory's Regulations would be developed. The regulations were filed in April 2013 and adopted in May 2013, with required sepsis protocol submission by September 1, 2013 and sepsis protocol implementation by December 31, 2013. Mandated reporting by hospitals began in the second quarter of 2014 and hospitals received their first data feedback from the New York State Department of Health in the third quarter of 2014. Because of the long lead time when hospitals could anticipate the policy change, and the staggered introduction of the policy's various elements, we will not specify a single post-intervention date or phase-in period. Rather, we will specify a modified DiD model with indicators for each post-intervention quarter and we will not exclude any data as a phase-in period. We will consider the pre-intervention period to be from January 1, 2011 through March 31, 2013, before the filing of the regulations.

We will control for patient characteristics and hospital characteristics as described above. We will also control for seasonality based on calendar quarter (implemented as a "season" term alone and

interacted with the treatment indicator). Finally, we will control for a common pre-intervention temporal trend using a continuous time variable (quarter, not interacted with the treatment indicator). We will control for a temporal trend because we suspect there may be secular changes in outcomes over time across all states, independent of any intervention (11). If the common temporal trend is not significantly different from zero, we will refit our model without the continuous time variable for parsimony before testing our primary hypotheses.

This model will allow us to test if outcomes in New York deviate from the common pre-intervention trend by a greater amount than in control states. Similar to the simpler DiD model, interaction terms for the post-intervention quarters with the treatment indicator are included. Here, the point estimate on each interaction term is interpreted as the estimated effect of the intervention in the given post-intervention quarter, representing the difference in deviation from the pre-intervention trends between New York and control states in that quarter. We will jointly test the null hypothesis that all of the quarter specific estimates are equal to zero. If this hypothesis is not rejected, we will conclude that Rory's Regulations did not have a significant effect on the particular dependent variable of interest. If this hypothesis is rejected, we will conclude that the regulation had an impact and we will test the effect at each post-intervention quarter.

To allow a marginal causal interpretation of our model parameters, we will use a linear probability model for all analyses. We will also address non-standard variance-covariance structures, which may arise for two reasons. First, for binary outcomes, we will have heteroskedastic error terms since the variance is a quadratic function of the true event percentages and attains its maximum at 50% (12). Second, outcomes of patients within a hospital are expected to be correlated. We will account for these non-standard variance-covariance structures by using robust standard errors clustered at the hospital level. Due to limitations in identifying repeated patient visits in some control states, admissions will be treated as independent observations. All coefficients will be modelled as fixed effects.

The model specification is as follows, for patient i , in hospital j , at time t :

$$Y_{ijt} = \eta_0 + \eta_1 NY_j + \tau_0 Time_t + \sum_{p=1}^P (\alpha_p Post_{pt} + \beta_p (NY_j Post_{pt})) + \sum_{q=2}^4 (\phi_{0q} Season_q + \phi_{1q} (NY_j Season_q)) + \sum_{v=1}^V \lambda_v X_{vij} + \epsilon_{ijt}$$

where Y_{ijt} is the outcome of interest (e.g., mortality), NY_j is an indicator equal to 1 for hospitals in New York, $Time_t$ is a continuous time variable (in quarters) centered at the last pre-intervention quarter, $Post_{pt}$ is an indicator equal to 1 if time is the p^{th} post-intervention quarter, $Season_q$ is an indicator for season based on calendar quarter, X_{vij} are the patient- and hospital- level covariates to be adjusted for, and ϵ_{ijt} is a patient level error term.

XI. MODEL ASSUMPTIONS AND CONSIDERATIONS OF ALTERNATIVE MODELS

We will check three assumptions underlying our primary model: 1) constant composition, 2) parallel trends, and 3) consistency of sepsis coding over time.

Constant composition

The constant composition assumption requires that the composition of intervention and comparison groups be stable over time (12-14). Because we will limit our analysis to only comparable hospitals in New York and control states in both the pre-intervention and post-intervention periods, this assumption will be satisfied.

Parallel trends

The parallel trends assumption requires that New York and control states have parallel trends in the outcome variable in the absence of the intervention (12-14). We will test the assumption in the pre-intervention period by using a model with a treatment indicator, a continuous time variable (implemented as quarters), and the interaction of these two variables. In the parallel trends test model, we will also control for seasonality, patient characteristics, and hospital characteristics as described above. Here we will not include terms for post-intervention quarters since this analysis includes the pre-intervention period only. The coefficient of interest is from the interaction term, which measures the difference in time trend between New York and control states in the pre-intervention period. If we do not reject that the interaction term is zero, we do not find evidence against the parallel trends assumption and will proceed with a DiD approach.

The model to test the parallel trends assumption is:

$$Y_{ijt} = \eta_0 + \eta_1 NY_j + \tau_0 Time_t + \tau_1 (NY_j Time_t) + \sum_{q=2}^4 (\phi_{0q} Season_q + \phi_{1q} (NY_j Season_q)) + \sum_{v=1}^V \lambda_v X_{vij} + \epsilon_{ijt}$$

If we reject that the interaction term is zero, however, instead of a DiD model, we will use a comparative interrupted time series model to account for the potential difference in time trends in the pre-intervention period. This model extends our earlier specification by including a term for the interaction of the treatment indicator with the continuous time variable. The remainder of the model is the same and we will test the quarter specific estimates as outlined above.

The comparative interrupted time series model is:

$$Y_{ijt} = \eta_0 + \eta_1 NY_j + \tau_0 Time_t + \tau_1 (NY_j Time_t) + \sum_{p=1}^P (\alpha_p Post_{pt} + \beta_p (NY_{ij} Post_{pt})) + \sum_{q=2}^4 (\phi_{0q} Season_q + \phi_{1q} (NY_j Season_q)) + \sum_{v=1}^V \lambda_v X_{vij} + \epsilon_{ijt}$$

Consistency of sepsis coding over time

Because we are using administrative data to identify cases of sepsis, prior to our main analysis we will examine the association between the New York State sepsis policy and sepsis coding over time. If the sepsis mandate influenced patterns of sepsis coding in New York relative to control states, an analysis of sepsis outcomes may be biased. To examine for this possibility, we will apply a similar comparative

interrupted time series model to that described above, except with a different population and dependent variable. In this case, the population will be all adult general short stay acute care hospital admissions; the primary dependent variable will be an indicator for sepsis; and the independent variables of interest will be an indicator for New York versus control and an indicator for each post-intervention quarter, with interactions as specified previously. In this model, we will also control for seasonality, patient characteristics, and hospital characteristics as described above, except excluding organ failures present on admission and sepsis infection categories. In this analysis, our primary question is whether sepsis coding changed over time differently in New York versus control states. If we find clinically significant changes in sepsis coding over time across states, we will evaluate a series of alternative approaches, including selection models that can account for these differential changes.

XII. SUBGROUP ANALYSES

For each outcome, we will perform subgroup analyses based on age (<60, 60 to 69, 70 to 79, 80+), number of comorbidities (<3 vs ≥ 3), number of organ failures (≤ 2 vs > 2), emergency department use, hospital size (3 categories as specified above), hospital academic status (3 categories as specified above), and hospital sepsis volume (3 categories specified as tertiles or using natural cut-points from the literature (15), depending on the observed distribution). These subgroups reflect hypotheses that the regulations will have a greater positive impact in younger patients, patients with fewer comorbid conditions, patients with greater numbers of organ failures, patients admitted from the emergency department, larger hospitals, academic hospitals, and high-volume hospitals.

To examine heterogeneity of the intervention effect within each subgroup of interest, we will extend our main model by including a categorical subgroup variable as well as interaction terms of subgroup with the treatment indicator, the continuous quarter variable, and each post-intervention quarter indicator, as well as a three-way interaction term with subgroup, the treatment indicator, and each post-intervention quarter indicator.

The coefficients of interest are from the interaction terms of the treatment indicator with the post-intervention quarter indicators (reference group value) and the three-way interaction terms (non-reference group values). We will test the homogeneity of the intervention effect with a joint null hypothesis that the coefficient on the three-way interaction term is zero for all non-reference subgroups and post-intervention quarters. If we reject the joint null hypothesis, we will have evidence that there is heterogeneity of the intervention effect across the subgroups on the given outcome. In that case, we will calculate and test subgroup-specific intervention effect estimates.

The subgroup analysis model is:

$$\begin{aligned}
Y_{ijt} = & \eta_0 + \eta_1 NY_j + \tau_0 Time_t + \sum_{p=1}^P (\alpha_p Post_{pt} + \beta_p (NY_j Post_{pt})) \\
& + \sum_{g=1}^{G-1} (\gamma_{0g} Subgroup_g + \gamma_{1g} (NY_j Subgroup_g)) + \sum_{g=1}^{G-1} (\theta_{0g} Subgroup_g Time_t) \\
& + \sum_{p=1}^P \sum_{g=1}^{G-1} (\psi_{gp} Post_{pt} Subgroup_g + \omega_{gp} (NY_j Post_{pt} Subgroup_g)) \\
& + \sum_{q=2}^4 (\phi_{0q} Season_q + \phi_{1q} (NY_j Season_q)) + \sum_{v=1}^V \lambda_v X_{vij} + \epsilon_{ijt}
\end{aligned}$$

where $Subgroup_g$ is the indicator for the subgroup level g , $g = 1, \dots, G$ where G is the total number of levels.

XIII. SENSITIVITY ANALYSES

We will perform several sensitivity analyses to examine the robustness of our results to study assumptions. First, we will repeat our main analysis using the modified Angus definition for sepsis, a broader criterion than our primary definition (16). The subset of patients identified from this definition is less likely to change over time due to coding practices, but the broader definition may identify more patients who are not eligible for the care processes outlined in Rory's Regulations (6). Second, we will repeat our main analysis including only patients with a diagnosis of severe sepsis or septic shock, a narrower criterion than our primary definition. While these patients are more likely to be eligible for the care processes outlined in Rory's Regulations, changes in coding practices over time are also more likely.

Third, we will repeat our main analysis excluding hospitals that participated in the United Hospital Fund and Greater New York Hospital Association's STOP-SEPSIS initiative, a sepsis-focused regional quality improvement initiative which began in 2010. The initiative was a protocol-based approach to case identification and rapid treatment. United Hospital Fund reported that participating hospitals saw an absolute reduction in inpatient mortality from severe sepsis of 22 percent from January 2011 to September 2012, better identification of sepsis, and better sepsis resuscitation in the emergency department. In the setting of high base-line performance on performance measures also addressed in Rory's Regulations, including these hospitals might reduce the potential for policy-related improvements and therefore influence our results.

Fourth, we will repeat our main analysis by moving the pre-intervention period back by two quarters to further account for anticipatory policy changes.

XIV. OTHER CONSIDERATIONS

Patients may be admitted multiple times in our cohort, but patient identifiers are not available in all control states. We anticipate that the outcomes of each admission may be approximately independent due to varying reasons for admission and treatment patterns. Thus, we will treat each admission as an independent record. To assess how reasonable this assumption is, we will quantify the within-person correlation using the intra-class-correlation (ICC) coefficient from an analysis using only the states in which patient identifiers are available.

XV. ROLE OF THE FUNDER AND POLICY SPONSOR

This work is funded by a research project grant from the United States Agency for Healthcare Research and Quality. The policy under evaluation was issued by the New York State Department of Health. All decisions about this analysis were made by the study investigators without input from the funder or policy sponsor. Dr. Kahn, the principle investigator of this study, takes full responsibility for the contents of this document.

XVI. POST-ANALYSIS DISSEMINATION

We will submit the results of this analysis for publication in the peer reviewed medical literature. Because this work is funded by the United States Department of Health and Human Services, the results will be made publicly available via PubMed Central, a service of the National Institutes of Health's National Library of Medicine.

XVII. REFERENCES

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