Economic analysis of mandated protocolized sepsis care in New York hospitals

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SUPPLMENTARY METHODS

I. Deviations from the pre-specified analysis plan and their rationale

In an effort to support the rigor and transparency of our results, we pre-published our complete statistical analysis plan on Open Science Framework (https://osf.io/jcwdv/) prior to analyzing the cost data. In our pre-published plan we acknowledged the possibility that we might need to alter our plans due to unforeseen circumstances. Here, we provide the details of such instances, along with the rationale for the changes.

1. Decision to not categorize hospitals by CHA membership status in creating a homogenous sample of hospitals across states. In the pre-published statistical analysis plan, we included Children's Hospital Association membership as one of the characteristics we would use to help create a homogenous sample of hospitals across states. We included this characteristic to help equalize hospitals that treated large numbers of children in New York and control states, among the other characteristics. However, with inclusion of this characteristic, only two hospitals were excluded: two CHA member hospitals with a combined sepsis case load of nearly 10,000 adults and 1,000 children. Because these two hospitals treated more adults than children by an order of magnitude, we decided to drop the variable from this step, enabling inclusion of these hospitals in the final analysis.

2. Decision to not include total ICU cost per stay and total ICU cost per day as secondary outcomes. In the pre-published statistical analysis plan, we included two additional secondary outcomes: total ICU cost per stay and total ICU cost per day. However, once we analyzed the charge variables available in the HCUP data, we realized that while ICU room charges could be determined, total ICU charges could not. Therefore, we were unable to include these outcomes.

II. Excluding hospital types that were not shared in both New York State and control states

To create a more homogenous sample of hospitals across states, we categorized hospitals based on the following characteristics: bed size (<100, 100 to 250, or >250); academic status (teaching [any resident full-time-equivalents] vs non-teaching); and regional population (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 two to three categories for each characteristic, there were a total of 3x2x3=18 possible characteristic combination groups. We excluded hospitals in groups that appeared only in the control states or only in New York State, in either the pre-intervention period or in the post-intervention period. The goal of this process was to exclude "outlier" hospital types and ensure that we could adequately control for hospital characteristics in the multivariable models.

III. Covariates

Patient-level variables for case-mix adjustment included age, gender, race, emergency department utilization, transfer from an acute care hospital, organ failures present on admission in the manner of Elias (Elias et al. Critical Care Medicine, 2005), sepsis infection categories in the manner of Ames (Ames et al., Pediatric Critical Care Medicine, 2018), and categorical comorbidity count (0, 1, 2, or 3+), with comorbidities defined in the manner of Elixhauser in adult

patients (Quan Medical Care, 2005) and Feudtner in pediatric patients (Feudtner Pediatrics 2000). To prevent bias by variation in coding patterns across states, we retained a maximum of 25 diagnosis codes and 15 procedure codes in each state and year. Hospital-level variables for case-mix adjustment included categorical variables for Children's Hospital Association membership, hospital size based on number of beds, hospital academic status based on resident-to-bed ratio, and geographical region population.

IV. Detailed model specifications

To understand the association between the regulation and hospital costs, we used a comparative interrupted time series approach. This approach tests if outcomes in New York deviated from a pre-intervention trend by a greater amount than in control states. We considered the pre-intervention period to be from January 1, 2011 through March 31, 2013, i.e. the period of time before the official filing of the regulations. The base model includes a continuous time variable (allowing for secular changes in outcome over time, independent of any intervention), an interaction term between the continuous time variable and treatment (allowing for the pre-intervention trends to differ between New York and control states), indicators for each post-intervention quarter (representing quarter-specific estimates in the post-intervention period), and a term for the interaction between the indicators and treatment (allowing the quarter-specific estimates to vary across New York and control states). The model also controls for patient characteristics and hospital characteristics described above, as well as seasonality based on calendar quarter (implemented as a "season" term alone and interacted with the treatment indicator).

This model is specified as:

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

where Y_{ijt} is the outcome of interest (e.g., cost per hospitalization), 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.

In this model the point estimate on each interaction term (β_p) is interpreted as the estimated association between the regulations and hospital costs 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. As the primary test of the association between the regulations and patient outcomes, we performed a joint test of the null hypothesis that all of the quarter specific estimates were equal to zero.

We used robust standard errors clustered at the hospital level to account for non-standard variance-covariance structures that might have arisen because hospital costs within a hospital are expected to be correlated. Due to limitations in identifying repeated patient visits in some

control states, admissions were treated as independent observations. All coefficients were modelled as fixed effects.

This comparative interrupted time series approach offers several benefits over more traditional approaches such as a difference-in-differences model. First, this approach does not require us to assume that the association between the regulations and hospital costs is constant over time or to exclude data from a phase-in period of an arbitrary length. Rather, it allows the association between an intervention and outcomes to differ over time as the different elements are rolled out without excluding any data as a phase-in period. Put another way, this model would allow the association between the intervention and outcomes to be small initially and increase over time, or be large initially and wane with time. This decision is important because the introduction and implementation of Rory's Regulations was staged, spanning several years.

This approach does not require us to assume that the pre-intervention trends are parallel between New York and control states. Although we carefully chose our control states based on their similarities to New York in terms of their demographics and policy landscapes, it was still possible that pre-intervention trends in outcomes might differ over time, necessitating a more flexible approach.

SUPPLEMENTARY TABLES

Supplemental Table 1. Subgroup analysis by age. The table shows the adjusted quarter and group-specific cost differences between New York and control states, with 95% confidence intervals.

	Age group	
	<18	**≥18**
N (New York)	3,928	326,357
N (Control)	5,690	690,698
Post-regulation quarter		
1 (4/1/13 – 6/30/13)	6,913 (-31,881 - 45,706)	1,727 (-289 - 3,743)
2 (7/1/13 – 9/30/13)	13,435 (-24,358 - 51,228)	1,252 (-758 - 3,262)
3 (10/1/13 – 12/31/13)	31,113 (-20,800 - 83,025)	689 (-1,577 - 2,954)
4 (1/1/14 – 3/21/14)	65,204 (12,009 - 118,400)	-471 (-3,020 - 2,077)
5 (4/1/14 – 6/30/14)	55,621 (-7,300 - 118,542)	2,018 (-1,173 - 5,208)
6 (7/1/14 – 9/30/14)	16,767 (-25,942 - 59,477)	1,696 (-1,580 - 4,972)
7 (10/1/14 – 12/31/14)	25,038 (-30,663 - 80,738)	1,626 (-1,388 - 4,641)
8 (1/1/15 – 3/21/15)	54,851 (-3,109 - 112,812)	2,211 (-1,451 - 5,873)
9 (4/1/15 – 6/30/15)	63,203 (-6,612 - 133,017)	1,829 (-2,029 - 5,688)
10 (7/1/15 – 9/30/15)	80,109 (2,437 - 157,781)	2,805 (-1,149 - 6,759)
Joint test of significance [a]	p = 1.00	

Values are the comparative interrupted time series estimates. Estimates adjust for all patient and hospital characteristics as well as pre-regulation temporal trends and season. Estimates are interpreted as the difference between the adjusted outcome and the adjusted counterfactual trend in New York compared to control states in that quarter. All costs are adjusted for inflation using the consumer price index and are presented in 2019 US dollars.

[a] P-value is for the hypothesis test examining whether, across all post-regulation quarters, any of the non-base category subgroup triple interaction terms differ from zero. This p-value is adjusted for multiple comparisons using the Bonferroni correction, where n=3 since there are 3 subgroup analyses. A significant p-value indicates the presence of variation in the association between the regulations and cost by subgroup.

Supplemental Table 2. Subgroup analysis by emergency department use. The table shows the adjusted quarter and group-specific cost differences between New York and control states, with 95% confidence intervals.

	Emergency department use	
	No	**Yes**
N (New York)	45,662	284,623
N (Control)	76,302	620,077
Post-regulation quarter		
1 (4/1/13 – 6/30/13)	4,717 (-1,415 - 10,848)	1,371 (-595 - 3,338)
2 (7/1/13 – 9/30/13)	6 (-8,117 - 8,128)	1,592 (-565 - 3,749)
3 (10/1/13 – 12/31/13)	63 (-10,400 - 10,526)	1,016 (-1,035 - 3,067)
4 (1/1/14 – 3/21/14)	1,183 (-9,626 - 11,991)	108 (-2,446 - 2,662)
5 (4/1/14 – 6/30/14)	7,359 (-5,873 - 20,592)	1,816 (-1,187 - 4,820)
6 (7/1/14 – 9/30/14)	-453 (-13,125 - 12,219)	2,085 (-994 - 5,163)
7 (10/1/14 – 12/31/14)	3,057 (-9,853 - 15,968)	1,495 (-1,474 - 4,464)
8 (1/1/15 – 3/21/15)	6,227 (-6,711 - 19,164)	2,246 (-1,589 - 6,081)
9 (4/1/15 – 6/30/15)	4,620 (-10,034 - 19,275)	2,137 (-1,668 - 5,941)
10 (7/1/15 – 9/30/15)	7,976 (-7,065 - 23,017)	2,920 (-989 - 6,830)
Joint test of significance [a]	p = 1.00	

Values are the comparative interrupted time series estimates. Estimates adjust for all patient and hospital characteristics as well as pre-regulation temporal trends and season. Estimates are interpreted as the difference between the adjusted outcome and the adjusted counterfactual trend in New York compared to control states in that quarter. All costs are adjusted for inflation using the consumer price index and are presented in 2019 US dollars.

[a] P-value is for the hypothesis test examining whether, across all post-regulation quarters, any of the non-base category subgroup triple interaction terms differ from zero. This p-value is adjusted for multiple comparisons using the Bonferroni correction, where n=3 since there are 3 subgroup analyses. A significant p-value indicates the presence of variation in the association between the regulations and cost by subgroup.

Supplemental Table 3. Subgroup analysis by Children's Hospital Association membership. The table shows the adjusted quarter and group-specific cost differences between New York and control states, with 95% confidence intervals.

	CHA Membership	
	No	**Yes**
N (New York)	240,874	89,411
N (Control)	553,768	142,611
Post-regulation quarter		
1 (4/1/13 – 6/30/13)	499 (-1,255 - 2,253)	5,358 (1,160 - 9,556)
2 (7/1/13 – 9/30/13)	1,465 (-537 - 3,466)	2,611 (-2,555 - 7,777)
3 (10/1/13 – 12/31/13)	925 (-1,481 - 3,331)	1,624 (-4,565 - 7,813)
4 (1/1/14 – 3/21/14)	-877 (-2,982 - 1,227)	3,687 (-4,666 - 12,040)
5 (4/1/14 – 6/30/14)	1,207 (-1,510 - 3,924)	7,427 (-2,115 - 16,969)
6 (7/1/14 – 9/30/14)	2,322 (-451 - 5,095)	1,891 (-7,704 - 11,485)
7 (10/1/14 – 12/31/14)	1,068 (-1,585 - 3,721)	4,023 (-5,169 - 13,215)
8 (1/1/15 – 3/21/15)	2,116 (-889 - 5,121)	5,036 (-5,980 - 16,052)
9 (4/1/15 – 6/30/15)	1,422 (-2,052 - 4,896)	6,285 (-5,365 - 17,935)
10 (7/1/15 – 9/30/15)	3,017 (-568 - 6,602)	7,720 (-4,682 - 20,123)
Joint test of significance [a]	p = 0.003	

Values are the comparative interrupted time series estimates. Estimates adjust for all patient and hospital characteristics as well as pre-regulation temporal trends and season. Estimates are interpreted as the difference between the adjusted outcome and the adjusted counterfactual trend in New York compared to control states in that quarter. All costs are adjusted for inflation using the consumer price index and are presented in 2019 US dollars.

[a] P-value is for the hypothesis test examining whether, across all post-regulation quarters, any of the non-base category subgroup triple interaction terms differ from zero. This p-value is adjusted for multiple comparisons using the Bonferroni correction, where n=3 since there are 3 subgroup analyses. A significant p-value indicates the presence of variation in the association between the regulations and cost by subgroup.

Supplementary Table 4. Sensitivity analysis excluding New York City area hospitals that had previously participated in a region-wide sepsis quality improvement initiative (i.e. the Greater New York Hospital Association [GNYHA] STOP-sepsis quality improvement initiative). The table shows the adjusted quarter-specific cost differences between New York and control states, with 95% confidence intervals.

	Patients in non-GNYHA hospitals
N (New York)	**150,908**
N (Control)	**696,379**
Post-regulation quarter	
1 (4/1/13 – 6/30/13)	2,190 (-1,035 to 5,415)
2 (7/1/13 – 9/30/13)	1.313 (-1,100 to 3,727)
3 (10/1/13 – 12/31/13)	528 (-2,542 to 3,597)
4 (1/1/14 – 3/21/14)	-575 (-2,911 to 1,761)
5 (4/1/14 – 6/30/14)	2,741 (-1,242 to 6,724)
6 (7/1/14 – 9/30/14)	3,106 (-310 to 6,523)
7 (10/1/14 – 12/31/14)	1,746 (-2,024 to 5,516)
8 (1/1/15 – 3/21/15)	4,124 (325 to 7,923)
9 (4/1/15 – 6/30/15)	3,587 (-913 to 8,087)
10 (7/1/15 – 9/30/15)	5,214 (353 to 10,075)
Joint test of significance [a]	p = 0.02

Values are the comparative interrupted time series estimates. Estimates adjust for all patient and hospital characteristics as well as pre-regulation temporal trends and season. Estimates are interpreted as the difference between the adjusted outcome and the adjusted counterfactual trend in New York compared to control states in that quarter. All costs are adjusted for inflation using the consumer price index and are presented in 2019 US dollars

[a] P-value is for the hypothesis test examining whether, across all post-regulation quarters, any of the interaction terms differ from zero.

Supplementary Table 5. Sensitivity analyses limiting control states to those with pre-intervention trends that were most similar to New York. The table shows the adjusted quarter-specific cost differences between New York and control states, with 95% confidence intervals.

	Controls: MA, NJ, FL	**Controls: NJ, FL**	**Control: NJ**
N (New York)	**330,285**	**330,285**	**330,285**
N (Control)	**587,024**	**479,796**	**145,003**
Post-regulation quarter			
1 (4/1/13 – 6/30/13)	2,215 (190 to 4,240)	2,230 (159 to 4,302)	988 (-1,925 to 3,902)
2 (7/1/13 – 9/30/13)	1,367 (-758 to 3,491)	1,406 (-844 to 3,655)	16 (-3,164 to 3,195)
3 (10/1/13 – 12/31/13)	1,574 (-808 to 3,956)	1,273 (-1,131 to 3,677)	902 (-2,476 to 4,280)
4 (1/1/14 – 3/21/14)	587 (-2,407 to 3,581)	267 (-2,835 to 3,369)	428 (-4,057 to 4,912)
5 (4/1/14 – 6/30/14)	3,252 (-237 to 6,742)	3,163 (-430 to 6,756)	2,450 (-2,631 to 7,531)
6 (7/1/14 – 9/30/14)	1,976 (-1,497 to 5,450)	1,922 (-1,671 to 5,516)	1,462 (-3,876 to 6,799)
7 (10/1/14 – 12/31/14)	2,345 (-973 to 5,662)	1,842 (-1,617 to 5,302)	1,947 (-3,199 to 7,093)
8 (1/1/15 – 3/21/15)	3,071 (-921 to 7,064)	2,577 (-1,531 to 6,685)	1,494 (-4,799 to 7,786)
9 (4/1/15 – 6/30/15)	3,517 (-767 to 7,801)	3,134 (-1,276 to 7,543)	2,644 (-4,097 to 9,385)
10 (7/1/15 – 9/30/15)	3,937 (-563 to 8,438)	3,620 (-1,048 to 8,287)	2,995 (-4,303 to 10,292)
Joint tests of significance [a]	p = 0.17	p = 0.19	p = 0.87

Values are the comparative interrupted time series estimates. Estimates adjust for all patient and hospital characteristics as well as pre-regulation temporal trends and season. Estimates are interpreted as the difference between the adjusted outcome and the adjusted counterfactual trend in New York compared to control states in that quarter. All costs are adjusted for inflation using the consumer price index and are presented in 2019 US dollars

[a] P-value is for the hypothesis test examining whether, across all post-regulation quarters, any of the interaction terms differ from zero.

Supplementary Table 6. Sensitivity analyses including interaction terms between all patient covariates and age. The table shows the adjusted quarter-specific cost differences between New York and control states, with 95% confidence intervals.

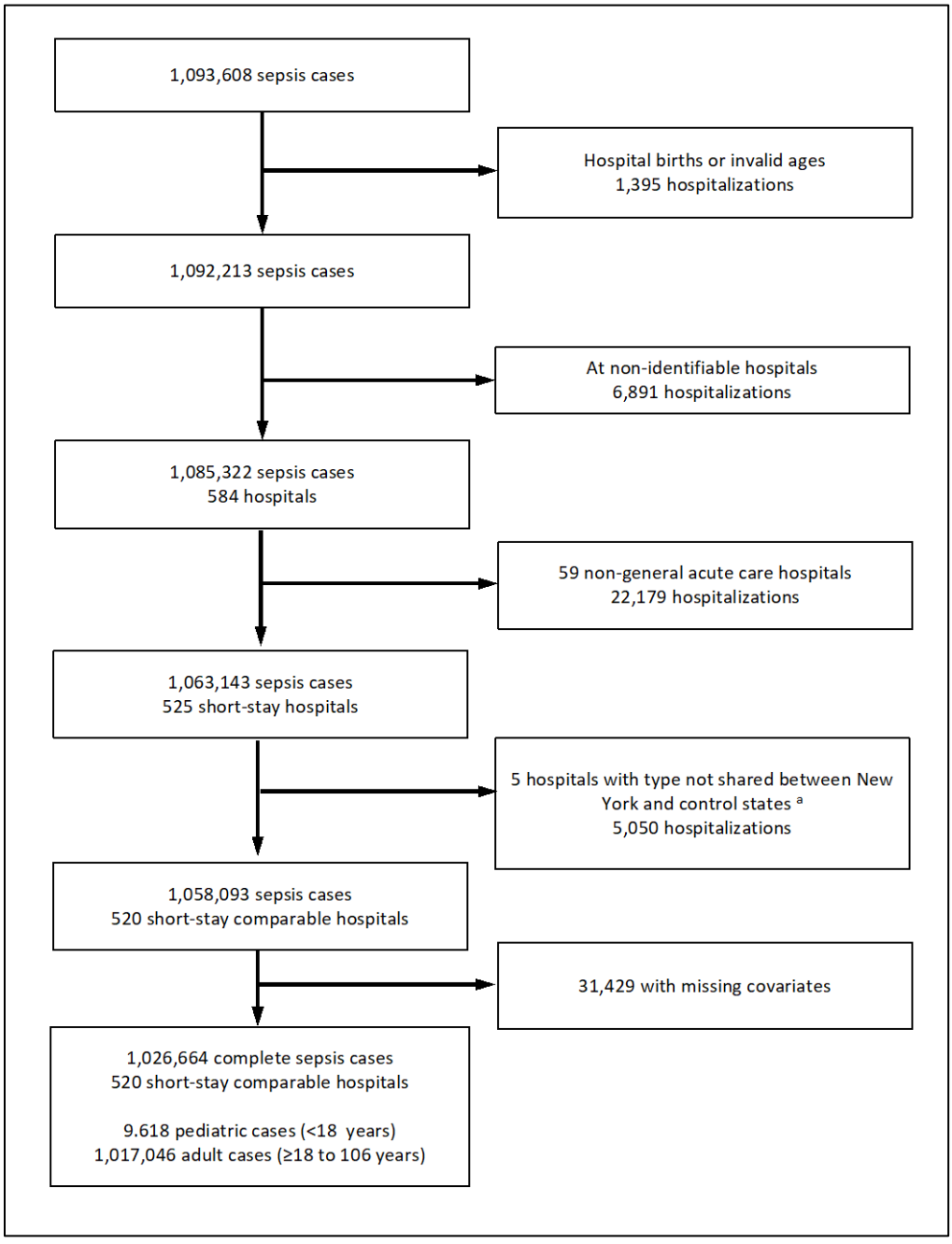
	Age interactions
N (New York)	**330,285**
N (Control)	**696,379**
Post-regulation quarter	**Estimate (95%CI)**
1 (4/1/13 – 6/30/13)	1,813 (-148 to 3,775)
2 (7/1/13 – 9/30/13)	1,514 (-496 to 3,525)
3 (10/1/13 – 12/31/13)	1,012 (-1,294 to 3,318)
4 (1/1/14 – 3/21/14)	291 (-2,592 to 3,174)
5 (4/1/14 – 6/30/14)	2,786 (-645 to 6,217)
6 (7/1/14 – 9/30/14)	1,881 (-1,441 to 5,203)
7 (10/1/14 – 12/31/14)	1,819 (-1,282 to 4,921)
8 (1/1/15 – 3/21/15)	2,880 (-898 to 6,658)
9 (4/1/15 – 6/30/15)	2,655 (-1,429 to 6,738)
10 (7/1/15 – 9/30/15)	3,685 (-512 to 7,882)
Joint test of significance [a]	p = 0.09

Values are the comparative interrupted time series estimates. Estimates adjust for all patient and hospital characteristics as well as pre-regulation temporal trends and season. Estimates are interpreted as the difference between the adjusted outcome and the adjusted counterfactual trend in New York compared to control states in that quarter. All costs are adjusted for inflation using the consumer price index and are presented in 2019 US dollars

[a] P-value is for the hypothesis test examining whether, across all post-regulation quarters, any of the interaction terms differ from zero.

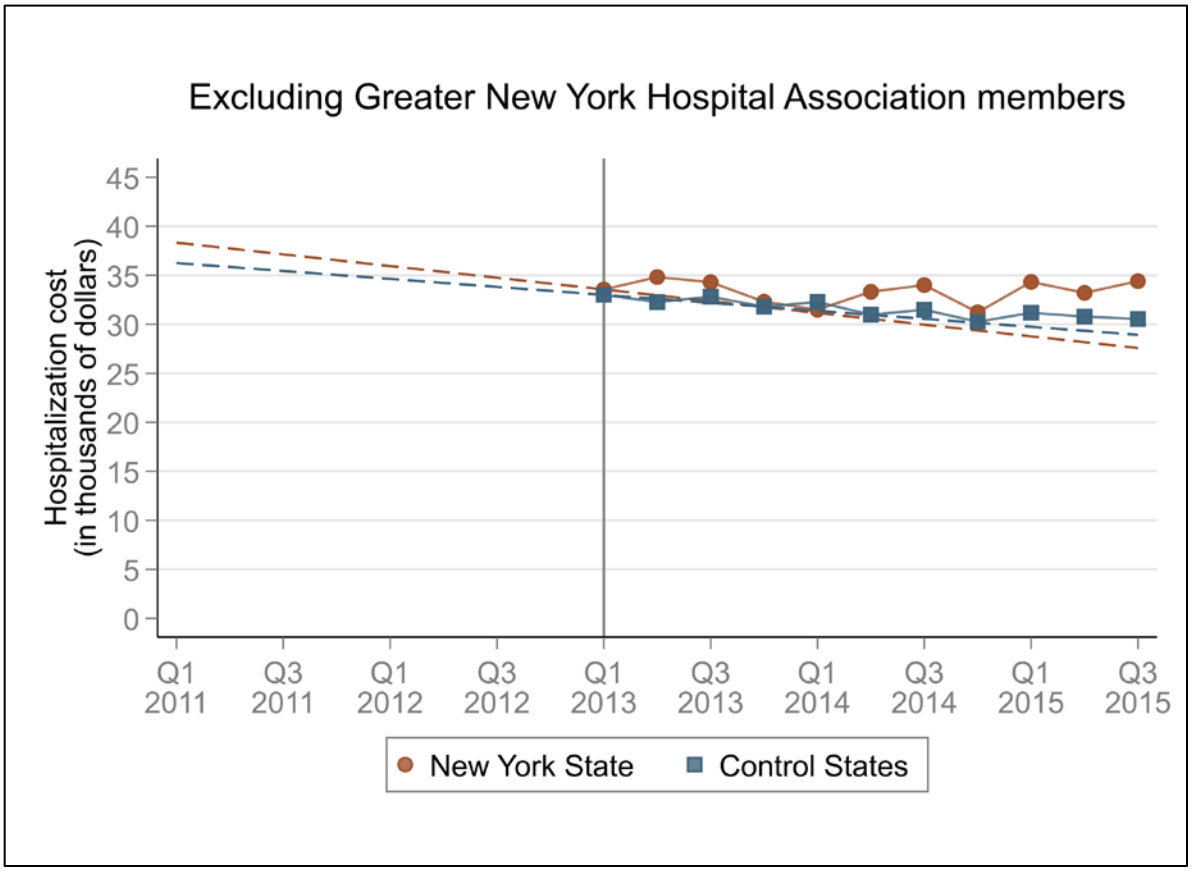
SUPPLEMENTARY FIGURES

Supplementary Figure 1. Patient flow diagram.

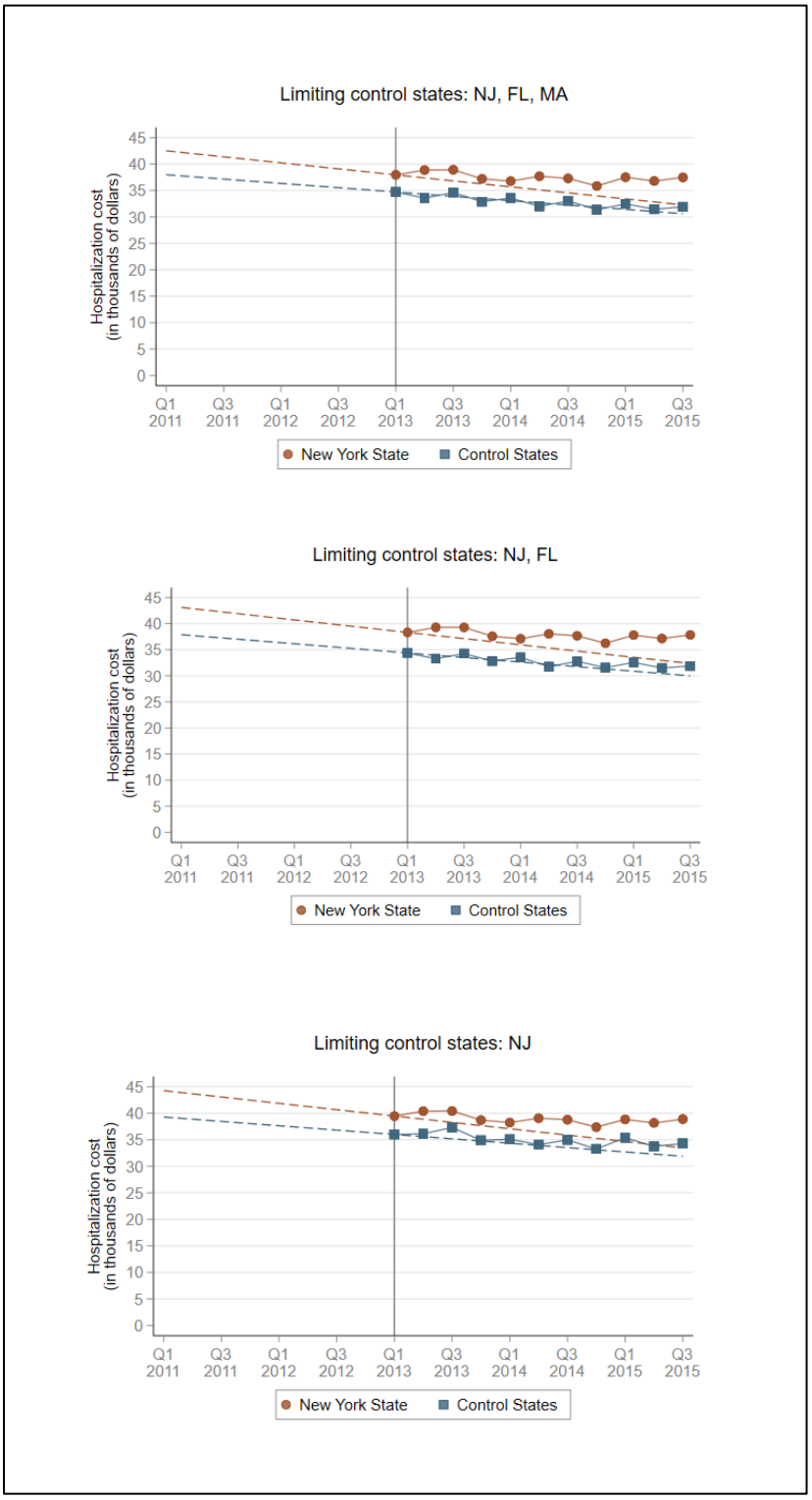


[a] Hospitals in 2 strata were excluded because of a lack of comparable hospitals. The strata were: (a) 100 to 250 beds, teaching, small MSA (4 New York hospitals) and (b) <100 beds, teaching, medium MSA (1 New York hospital).

Supplementary Figure 2. Sensitivity analysis excluding New York City area hospitals that had previously participated in a region-wide sepsis quality improvement initiative (i.e. the Greater New York Hospital Association STOP-sepsis quality improvement initiative).



Supplementary Figure 3. Sensitivity analyses limiting control states to those with pre-intervention trends that were most similar to New York. NJ = New Jersey; FL = Florida; MA = Massachusetts.



Supplementary Figure 4. Sensitivity analyses including interaction terms between all patient covariates and age.