# STRENGTHENING HEALTH SERVICES RESEARCH USING TARGET TRIAL EMULATION: AN APPLICATION TO VOLUME-OUTCOMES STUDIES

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## Web Appendix

**Web Appendix 1: Assignment mechanism for Target Trials #3 and #4**

Surgeons who performed fewer operations than the median volume of all surgeons during the pre-baseline interval (denoted by $\tilde{\mu}$) are assigned to add to their volume by $x$ cases (as in prior trials). For many surgeons with pre-baseline volume $w < \tilde{\mu}$, they will not be able to fully add to their volume when $x < -1$ and $|x| > w$; as such, each surgeon $j$ is assigned to perform $A_j = \max(0, w_j + x)$ as in trials #1 and #2. For surgeons with $w \geq \tilde{\mu}$ and $x \geq -1$, they are assigned to perform $w - x$ operations. However, for surgeons with $w \geq \tilde{\mu}$ and $x < -1$, fewer than $x$ cases will be available for each surgeon; specifically, only $\sum_{j:w_j<\tilde{\mu}} w_j - a_j < x \sum_{j=0}^{J} \mathbb{1}(w_j < \tilde{\mu})$ cases will be available. As such, when $x < -1$, surgeons with $w \geq \tilde{\mu}$ are randomly assigned to a volume $w_j - a_j$ for a randomly selected surgeon $j$ with $w < \tilde{\mu}$ such that the net number of operations will remain fixed at the pre-baseline level.

In summary, for intervention arm $x$ and pre-baseline volume $w_{(1)}, \ldots, w_{(J)}$ in ascending order with surgeons $j \in \{1, \ldots, J\}$, each surgeon's operative volume assignment will be

$$A_j = \begin{cases} \max(w_j + x, 0) & \text{if } \; w_j < \tilde{\mu} \\ \max(w_j - x, 0) & \text{if } \; w_j \geq \tilde{\mu} \; \text{ and } \; x \geq -1 \\ n_m & \text{if } \; w_j \geq \tilde{\mu} \; \text{ and } \; x < -1 \end{cases} \tag{1}$$

where $n_m$ for $m \in \{\lceil J/2 \rceil + 1, \ldots, J\}$ is defined by the following:

Let $\mathbf{k} = k_1, \ldots, k_{\lceil J/2 \rceil} = w_1 - a_1, \ldots, w_{\lceil J/2 \rceil} - a_{\lceil J/2 \rceil}$ and $\mathbf{k}^*$ be a random permutation of $\mathbf{k}$ : $k_1^* = k_{\pi(1)}, \ldots, k_{\lceil J/2 \rceil}^* = k_{\pi(\lceil J/2 \rceil)}$.

Then define $\mathbf{n} = \mathbf{k}^* = k_{\pi(1)}^*, \ldots, k_{\pi(\lceil J/2 \rceil)}^*$.

**Web Appendix 2: Inverse probability weights**

This section describes the estimation of stabilized inverse probability weights used in the main analysis:

$$SW = SW^A \cdot SW^C$$

$$SW^A = \prod_{k=0}^{K} \frac{f(A_k | A_{k-1}, V)}{f(A_k | A_{k-1}, \overline{L}_{k-1}, V)}$$

where $f(A_k | A_{k-1}, \overline{L}_{k-1}, V)$ is the conditional probability mass function $f_{A_k|A_{k-1},\overline{L}_{k-1},V}(a_k | a_{k-1}, \bar{l}_{k-1}, v)$ evaluated at the random expression $A_k | A_{k-1}, \overline{L}_{k-1}, V$ and, as described in the main text, $A$ is the sum of baseline volume $W$ and assignment $X$.

Additionally, because a one-interval deviation is permitted, the numerator and denominator are deterministically equal to 1 in the first interval $k = 0$ following consecutive adherence to the randomized assignment (all individuals are by convention considered to be adherent during interval $k = -1$).

To estimate the quantities in the numerator and denominator, under the assumption that the operative volume of a surgeon in any given interval ($A_k$) is a negative binomial random variable with non-constant dispersion, we fit the following discrete-time regressions:

$$\hat{\mathbb{E}}[A_k | A_{k-1}, V] = \exp\left(\theta_{0,k} + \theta_1^T h(a_k) + \theta_2^T V\right) \tag{2}$$

$$\hat{\mathbb{E}}[A_k | A_{k-1}, \overline{L}_{t-1}, V] = \exp\left(\theta_{0,k} + \theta_1^T h(a_k) + \theta_3^T \bar{l}_k + \theta_4 V\right) \tag{3}$$

where $\theta_{\cdot,k} = \theta_{\cdot}^T g(k)$ is a time-varying parameter and the overbar denotes a variable's history in the prior interval. The dispersions for Equations (2) and (3) are separately modeled using the same covariates, using gamma regression. Surgeon-specific mean and dispersion predictions for the numerator and denominator equations are then used to generate negative binomial distributions with which corresponding probabilities can be computed for each surgeon-specific observed value of $A_k$.

Finally, only surgeons who perform one or more operations during interval $K+1$ will have measurable outcomes during that interval. To account for this potential selection bias, the following stabilized censoring weights can be used:

$$SW^C = \frac{p(C_{K+1}=0|A_K, V)}{p(C_{K+1}=0|A_K, \overline{L}_K, V)}$$

where $C_{K+1}$ denotes censoring in interval $K+1$. The numerator and denominator of the weights can be estimated with the following discrete-time logistic regressions:

$$\hat{p}(C_{K+1}=0|A_K=a_K, V=v) = \text{expit}\big(\theta_0 + \theta_1^T h(a_k) + \theta_2^T v\big)$$

$$\hat{p}(C_{K+1}=0|A_K=a_K, \overline{L}_K=\overline{l}_K, V=v) = \text{expit}\big(\theta_0 + \theta_1^T h(a_k) + \theta_2^T \overline{l}_t + \theta_4 v\big)$$

**Web Appendix 3: Sensitivity analysis**

This section describes the estimation of stabilized inverse probability weights used in the main analysis:

$$SW = SW_K^A \cdot SW_{K+1}^C$$

**Treatment weights**

$$SW_t^A = \prod_{k=1}^{t} \frac{f(A_k|A_{k-1}, V, C_k=0)}{f(A_k|A_{k-1}, \overline{L}_{k-1}, V, C_k=0)} \tag{4}$$

We fit the same discrete-time regressions for the numerator and denominator as in the main analysis, now conditional on not having been censored ($\overline{C}_k = 0$) for deviating from the assignment a second time or performing zero operations in period $k$.

$$\mathbb{E}[A_k|A_{k-1}, V, \overline{C}_k=0] = \exp\left(\theta_{0,k} + \theta_1^T g(A_{k-1}) + \theta_2^T V\right) \tag{5}$$

$$\mathbb{E}[A_k|A_{k-1}, V, \overline{L}_{k-1}, \overline{C}_k=0] = \exp\left(\theta_{0,k} + \theta_1^T g(A_{k-1}) + \theta_2^T \overline{L}_k + \theta_3^T V\right) \tag{6}$$

where $\theta_{\cdot,k} = \theta_{\cdot}^T g(k)$ is a time-varying parameter, $g(\cdot)$ is a flexible function such as restricted cubic splines, and the overbar denotes a variable's history including the previous interval.

**Censoring weights**

After following the regime in each interval $k$, only surgeons who perform one or more operations during interval $k+1$ will have measurable outcomes during that interval. To account for this censoring, the following weights were used:

$$SW_t^C = \prod_{k=1}^{t} \frac{f(C_k|A_k, V, C_{k-1}=0)}{f(C_k|A_k, \overline{L}_k, V, C_{k-1}=0))} \tag{7}$$

The numerator and denominator of the surgeon-specific censoring weights were estimated with the following discrete-time logistic regression equations:

$$\mathbb{E}[C_k|V] = \exp\left(\theta_{0,k} + \theta_1 A_{k-1} + \theta_2^T V\right) \tag{8}$$

$$\mathbb{E}[C_k|A_{k-1}, \overline{L}_{k-1}, V] = \exp\left(\theta_{0,k} + \theta_1 A_{k-1} + \theta_2^T \overline{L}_{k-1} + \theta_4^T V\right) \tag{9}$$

**Standardization**

As described above, the time-fixed covariates were included in the numerators of the stabilized weights. These variables can be adjusted for using the following outcome regression, weighted by $SW$:

$$\mathbb{E}\big[\pi|X=x\big] = \sum_{w\in W, v\in V} \mathbb{E}\Big(\pi|X=x, W, V\Big)p(W=w, V=v) \tag{10}$$

$$= \hat{\mathbb{E}}_{w\in W, v\in V}\mathbb{E}\Big[\pi|X=x, W, V)\Big] \tag{11}$$

$$= \hat{\mathbb{E}}_{w\in W, v\in V}\text{expit}\big(\alpha_0 + \alpha_1 g(X) + \alpha_2^T V + \alpha_3^T W\big) \tag{12}$$

Interaction terms were additionally included between the intervention arm and all time-fixed covariates.

## Web Appendix 4: Consideration of positivity violations

In the Medicare data, eligible surgeons were observed to perform between 0 and 59 operations per interval. Among surgeons with a pre-baseline operative volume of 0-4, very few were observed to perform higher numbers of operations in the following interval. Conversely, among surgeons with a pre-baseline operative volume of 15 or greater, very few were observed to perform lower numbers of operations in the following interval. A summary of observed operative volumes for different pre-baseline operative volume histories is reported in Appendix Table **??**. Given this concern for non-random violations of positivity in the available observed data (especially when including other covariate patterns), we did not consider this trial further. These problems were magnified with a static sustained regime.

## Web Tables

**Web Table 1:** International Classification of Diseases (ICD) Codes

| ICD code | Revision version | Description |
|---|---|---|
| 361 | ICD-9 | Bypass anastomosis for heart revascularization |
| 362 | ICD-9 | Heart revascularization by arterial implant |
| 02100 | ICD-10 | Bypass coronary artery, one artery |
| 02110 | ICD-10 | Bypass coronary artery, two arteries |
| 02120 | ICD-10 | Bypass coronary artery, three arteries |
| 02130 | ICD-10 | Bypass coronary artery, four or more arteries |

**Web Table 2:** Example of expanded dataset and artificial censoring for emulation of Target Trial #2 (arms $x = 1$ and $x = 2$ shown; $K = 3$). Gray shading indicates intervals prior to eligibility assessment.

| Surgeon ID.clone | Arm | Interval | Operative volume | Change from pre-baseline volume ($x$) | Mortality proportion | Artificial censoring |
|---|---|---|---|---|---|---|
| #1.1 | - | -2 | 3 | - | 1/3 | 0 |
| #1.1 | - | -1 | 1 | - | 0/1 | 0 |
| #1.1 | $x = 1$ | 0 | 2 | 1 | 1/2 | 0 |
| #1.1 | $x = 1$ | 1 | 2 | 1 | 0/2 | 0 |
| #1.1 | $x = 1$ | 2 | 2 | 1 | 0/2 | 0 |
| #1.1 | $x = 1$ | 3 | 2 | 1 | 0/2 | 0 |
| #1.1 | $x = 1$ | 4 | 6 | 5 | 2/6 | 0 |
| #1.2 | - | -2 | 3 | - | 1/3 | 0 |
| #1.2 | - | -1 | 1 | - | 0/1 | 0 |
| #1.2 | $x = 2$ | 0 | 2 | 1 | 1/2 | 0 |
| #1.2 | $x = 2$ | 1 | 2 | 1 | 0/2 | 1 |
| #3.1 | - | -2 | 5 | - | 1/5 | 0 |
| #3.1 | - | -1 | 2 | - | 0/2 | 0 |
| #3.1 | $x = 1$ | 0 | 3 | 1 | 1/3 | 0 |
| #3.1 | $x = 1$ | 1 | 0 | -2 | 0 | 0 |
| #3.1 | $x = 1$ | 2 | 3 | 1 | 0/3 | 0 |
| #3.1 | $x = 1$ | 3 | 1 | -1 | 0/1 | 1 |
| #3.2 | - | -2 | 5 | - | 1/5 | 0 |
| #3.2 | - | -1 | 2 | - | 0/2 | 0 |
| #3.2 | $x = 2$ | 0 | 3 | 1 | 1/3 | 0 |
| #3.2 | $x = 2$ | 1 | 0 | 1 | 0 | 1 |

*Among patients who underwent an operation during the current interval.

**Web Table 3:** Positivity check for Target Trial #1

| Volume category | History: 0 to 4 | History: 5 to 9 | History: 10 to 14 | History: 15+ |
|---|---|---|---|---|
| -5 | 0 | 647 | 510 | 352 |
| -4 | 174 | 889 | 533 | 311 |
| -3 | 521 | 1288 | 587 | 318 |
| -2 | 1104 | 1496 | 611 | 284 |
| -1 | 1750 | 1493 | 592 | 238 |
| 0 | 1736 | 1486 | 521 | 246 |
| 1 | 1689 | 1327 | 499 | 193 |
| 2 | 1298 | 1051 | 383 | 176 |
| 3 | 982 | 867 | 309 | 157 |
| 4 | 695 | 616 | 276 | 118 |
| 5 | 456 | 454 | 193 | 93 |

**Web Table 4:** Positivity check for Target Trial #2

| Volume category | History: 0 to 4 | History: 5 to 9 | History: 10 to 14 | History: 15+ |
|---|---|---|---|---|
| -5 | 0 | 161 | 17 | 6 |
| -4 | 136 | 59 | 16 | 11 |
| -3 | 199 | 66 | 18 | 4 |
| -2 | 349 | 93 | 19 | 8 |
| -1 | 506 | 89 | 6 | 4 |
| 0 | 176 | 83 | 15 | 4 |
| 1 | 131 | 44 | 13 | 3 |
| 2 | 102 | 37 | 10 | 2 |
| 3 | 38 | 25 | 3 | 1 |
| 4 | 24 | 11 | 1 | 4 |
| 5 | 21 | 8 | 2 | 0 |

**Web Table 5:** Mortality estimates for sensitivity analysis of Target Trial #2 (IPW)

| Change in volume | 90-day mortality (%) |
|---|---|
| -5 | 6.8 (4.6-10.4) |
| -4 | 6.9 (5.4-8.9) |
| -3 | 6.8 (5.6-8.8) |
| -2 | 6.7 (5.4-8.7) |
| -1 | 6.6 (5.4-8.1) |
| 0 | 6.3 (5.5-7.2) |
| 1 | 5.9 (5.0-7.0) |
| 2 | 5.6 (4.5-6.8) |
| 3 | 5.2 (4.3-6.3) |
| 4 | 4.9 (3.7-6.3) |
| 5 | 4.5 (2.8-7.2) |