Latour et al. Supplemental Material

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Supplemental Methods 1. Justification for data generation parameters.

Below, we provide justification for the parameters used in this study to generate our simulation data.

Parameter/Generation	**Justification**
We randomly assigned patients to have "more-severe" or "less-severe" ITP with a probability of 0.5.	This was done to maintain a relatively even distribution of patients across ITP severity and subsequently sample size. We randomly generated this value to preserve as much randomness as possible.
We generated 200 platelet counts for each person.	This choice was made arbitrarily. Ultimately, we wanted to ensure sufficient sample size, as our primary concern was not performance of the methods in imbalanced settings, though this should be explored in other work.
Platelet counts were generated from normal distributions.	This distribution was used for simplicity and ease of generation and selection in the simulation. Ultimately, the underlying distribution will not impact the results shown in this study, as we're focused on the median platelet count, and the summary metric makes no assumptions about its underlying distribution.
We included patients into the cohort at $\leq 30\times10^9$/L that occurred after ≥8 platelet count measurements.	This cut point for inclusion mirrors the prior ITP study. 8 platelet counts was chosen arbitrarily. We wanted enough prior counts to understand the distribution. This reflects ideal settings, but likely should be explored further in real-world data.
Strongly and weakly differential RTM was generated using selection probabilities of 0.8/0.2 and 0.6/0.4, respectively.	These probabilities were defined as such to explore this source of bias in an extreme and non-extreme scenario. This was unknown in the prior study, as it was not measured.
Sample size of 200	This mirrored the prior ITP study
Sample size of 10,000	This was sufficiently large that we could run the analysis on servers and still understand if there were small sample concerns.
Treatment effect of 50×10^9/L	This mirrors the definition of durable platelet response (i.e., positive health outcome associated with therapy) in the original ITP study.

Supplemental Methods 2. Propensity score models.

For each scenario, we calculated 8 treatment effect estimates. Below, we describe the logistic regression model used to calculate each estimate.

Adjustment Metric for Underlying Immune ITP Severity	Logistic Regression Model[a]
(1) No Adjustment	No logistic regression model calculated.
(2) Platelet count mean prior to cohort entry	$Y = \beta_0 + \beta_1 \times \mu$ μ = Mean of the 8 platelet counts prior to cohort entry
(3) Platelet count standard deviation prior to cohort entry	$Y = \beta_0 + \beta_1 \times \sigma$ σ = Standard deviation of 8 platelet counts prior to cohort entry
(4) Difference between most recent prior platelet count and cohort entry event	$Y = \beta_0 + \beta_1 \times \Delta_{recent}$ Δ_{recent} = Difference between the most recent prior platelet count and the cohort entry event
(5) Difference between largest prior platelet count and cohort entry event	$Y = \beta_0 + \beta_1 \times \Delta_{largest}$ $\Delta_{largest}$ = Difference between the largest prior platelet count and the cohort entry event
(6) Platelet count mean and standard deviation prior to cohort entry	$Y = \beta_0 + \beta_1 \times \mu + \beta_2 \times \sigma$
(7) All summary measures calculated prior to cohort entry	$Y = \beta_0 + \beta_1 \times \mu + \beta_2 \times \sigma + \beta_3 \times \Delta_{recent} + \beta_4 \times \Delta_{largest}$
(8) Gold standard	$Y = \beta_0 + \beta_1 \times \eta$ η = A patients true disease severity value (i.e., more- or less-severe disease)

[a] Y = Probability of treatment with romiplostim.

Supplemental Methods 3. Estimator of Median Overall Platelet Count

For each treatment group, we first calculated $m(a)$, the counterfactual median overall platelet count in a population of patients with treatment $A = a$. We calculated $m(a)$ by solving the estimating equation below:

$$0 = 0.5 - \frac{1}{n}\sum_{i=1}^{n}\frac{1}{23}\sum_{j=2}^{24}\frac{I\left(Y_{i,j} < \hat{m}(a)\right)\Delta_{i,j}I(S_i = 1)I(A_i = a)I(M_i = 1)}{f_s\, f_\Delta \Pr\left(M_i = 1 \middle| A_i, \bar{W}_i, S_i = 1, \Delta_{i,j} = 1\right)}\boldsymbol{W}_i$$

where i indexes the observation under analysis, j indexes the week of follow-up that a patient platelet count measure was drawn, and *n* indicates the number of patients in the cohort. $Y_{i,j}$ represents the j^{th} platelet count for the i^{th} individual. $\bar{W}_i$ denotes the history of patient covariates (up to the time of censoring or event) and W_i are baseline covariates. S_i is an indicator that patient i does not have any missing baseline covariate data. $\Delta_{i,j}$ is an indicator that the j^{th} platelet count for the i^{th} individual was not censored. M_i is an indicator of having no missing platelet count data. Further, $f_s = \Pr(S_i = 1|W_{0i}^*)$ and $f_\Delta = Pr\left(\Delta_{i,j} = 1 \middle| A_i = a, \overline{W_i}, S_i = 1\right)$. The treatment effect was estimated as the difference between the median overall platelet counts of the two groups: $m(1) - m(a)$.

For the simulation analysis, W_i was calculated as a patient's inverse probability of treatment weight: 1/PS in the treatment group and 1/(1-PS) in the SOC group. Further, this analysis did not allow for missing data and was structured such that the only potential source of censoring was administrative. Thus, we set $f_s\, f_\Delta \Pr\left(M_i = 1 \middle| A_i, \bar{W}_i, S_i = 1, \Delta_{i,j} = 1\right), \Delta_{i,j}, I(S_i = 1)$, and $I(M_i = 1)$ all equal to 1. This estimating equation was minimized for a solution using the optimize function within the stats package in R.

References:

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

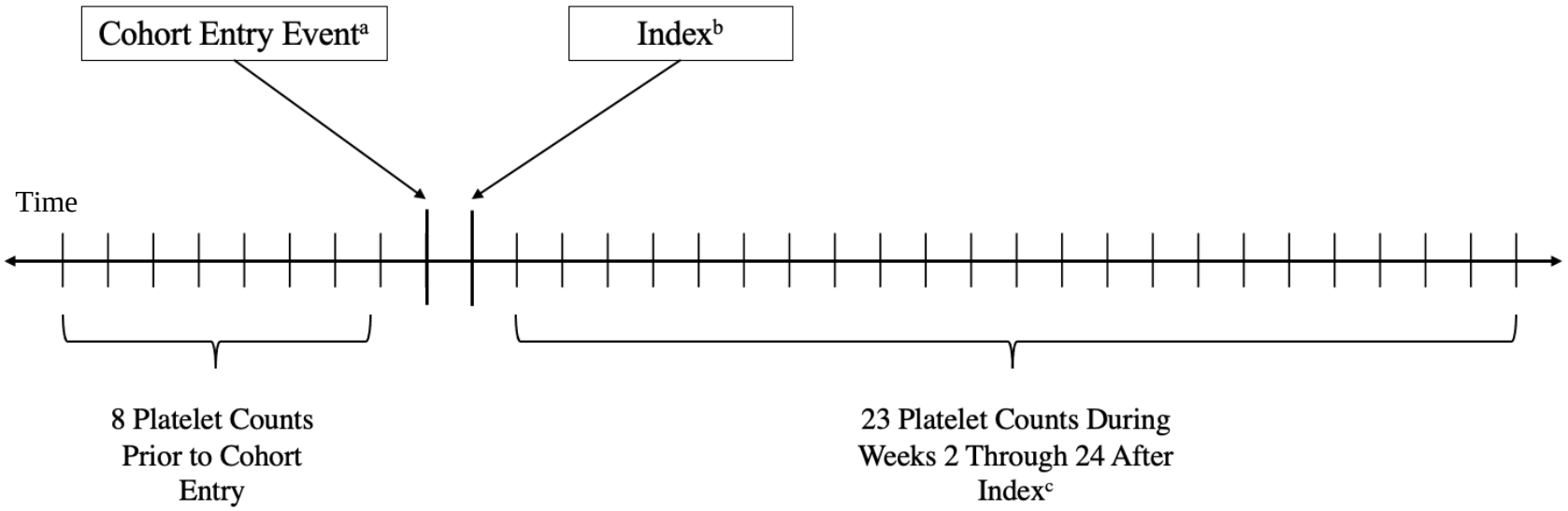
Supplemental Methods 4. Formulas used to calculate performance metrics, as defined by Morris et al. 2019.

Metric	Definition	Estimate
Bias[a]	$E[\hat{\theta}] - \theta$	$\frac{1}{n_{sim}} \sum_{i=1}^{n_{sim}} \hat{\theta}_i - \theta$
Empirical Standard Error	$\sqrt{Var(\hat{\theta})}$	$\sqrt{\frac{1}{n_{sim} - 1} \sum_{i=1}^{n_{sim}} (\hat{\theta}_i - \bar{\theta})^2}$
Mean Squared Error	$E[(\hat{\theta} - \theta)^2]$	$\frac{1}{n_{sim}} \sum_{i=1}^{n_{sim}} (\hat{\theta}_i - \theta)^2$

[a] We calculated confidence intervals for the average bias seen within a scenario as using the estimated bias ($\hat{\theta}$) and empirical standard error ($\hat{\sigma}$). The bounds were calculated as $\hat{\theta} \pm (z_{97.5} \times \hat{\sigma}/\sqrt{n})$, where $z_{97.5}$ represents the 97.5th percentile of a Normal probability distribution with mean 0 and standard deviation 1 (~1.96) and n represents the number of simulations (2,000).

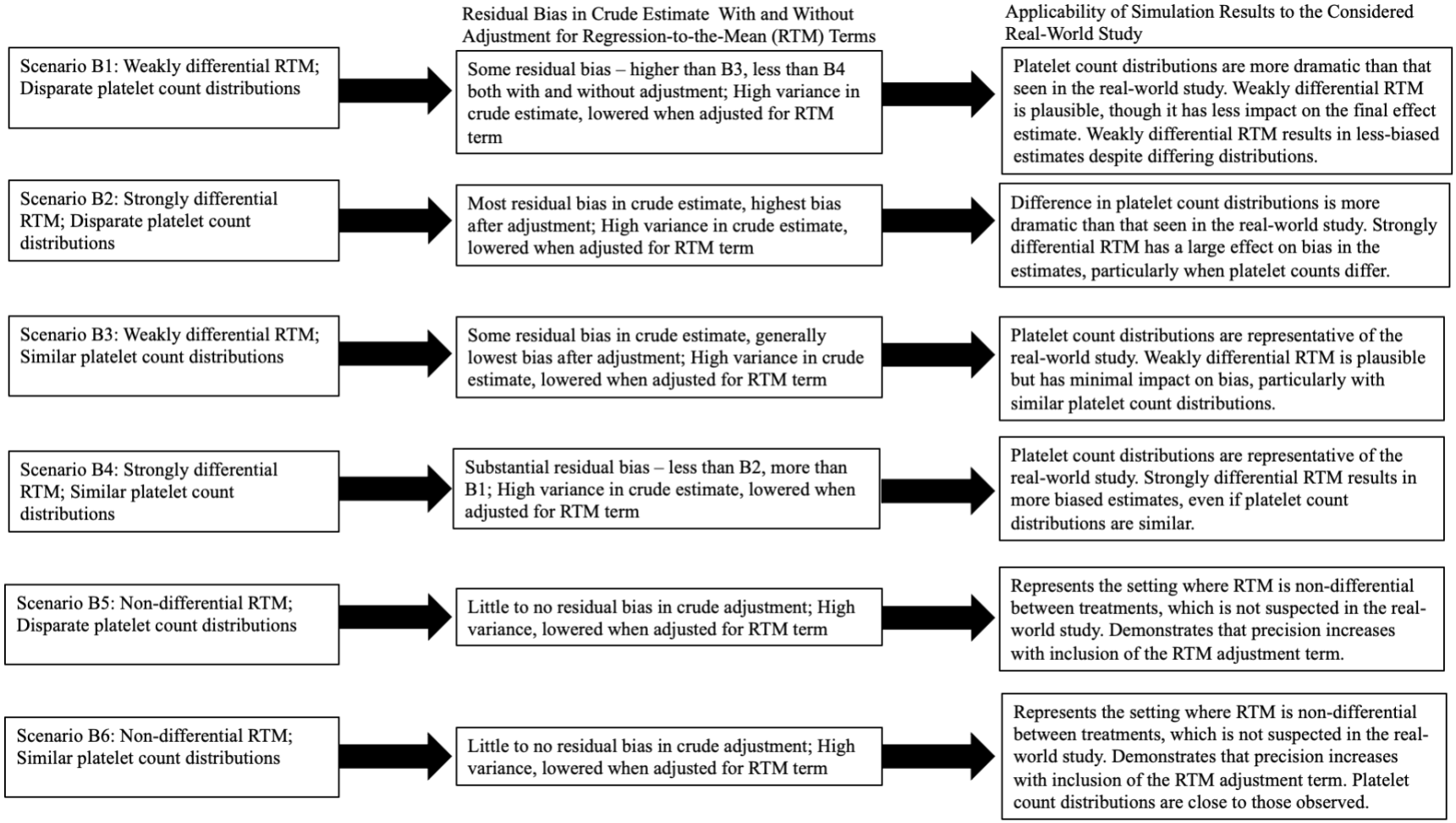
Figures Describing the Simulation Set-Up

Supplemental Figure 1. Schematic depicting the platelet counts analyzed for each simulated participant.



[a] The cohort entry event was defined as the first platelet count ≤30×10^9/L with at least 8 prior platelet counts.
[b] The index platelet count was defined as the first weekly platelet count after the anchor that was excluded from follow-up to allow a treatment effect.
[c] Additional platelet counts associated with a treatment effect are added to platelet counts from these weeks.

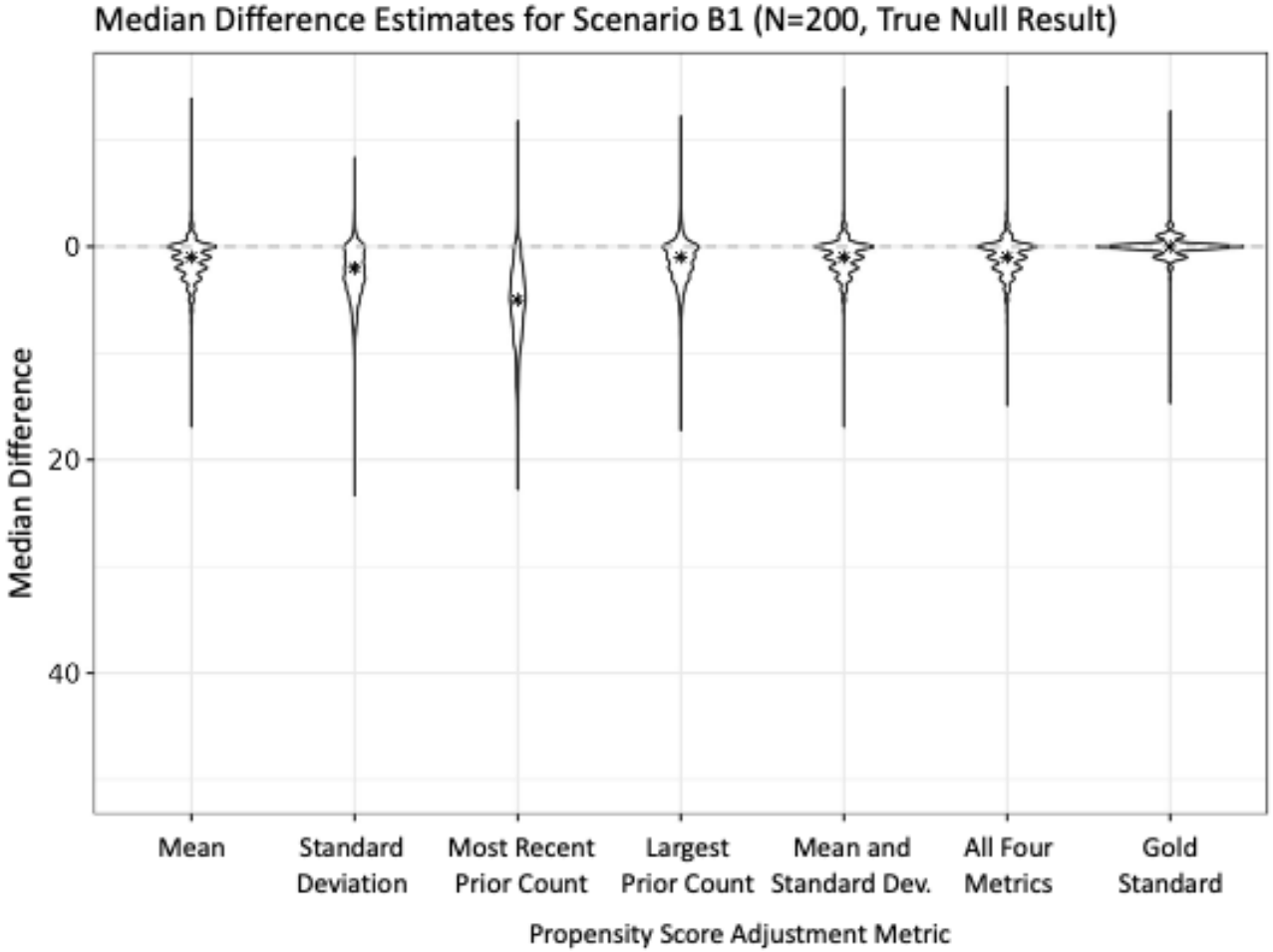
Supplemental Figure 2. Qualitative summary of results and conclusions made for scenarios B1 through B6. Conclusions apply for both null and non-null treatment effects and sample sizes of n=200 and n=10,000.



The strength of differential RTM refers to the probabilities used to select a patient's treatment based upon their predefined ITP severity strata. Strongly differential RTM corresponds to 0.8/0.2 treatment selection probabilities, weakly differential RTM to 0.6/0.4, and non-differential to 0.5/0.5. Platelet counts are derived for each patient from normal distributions with a predefined mean (μ) and standard deviation (σ). Similar platelet count distributions are defined by μ=55, σ=20 for the less-severe versus μ=35, σ=10 for the more-severe ITP strata.

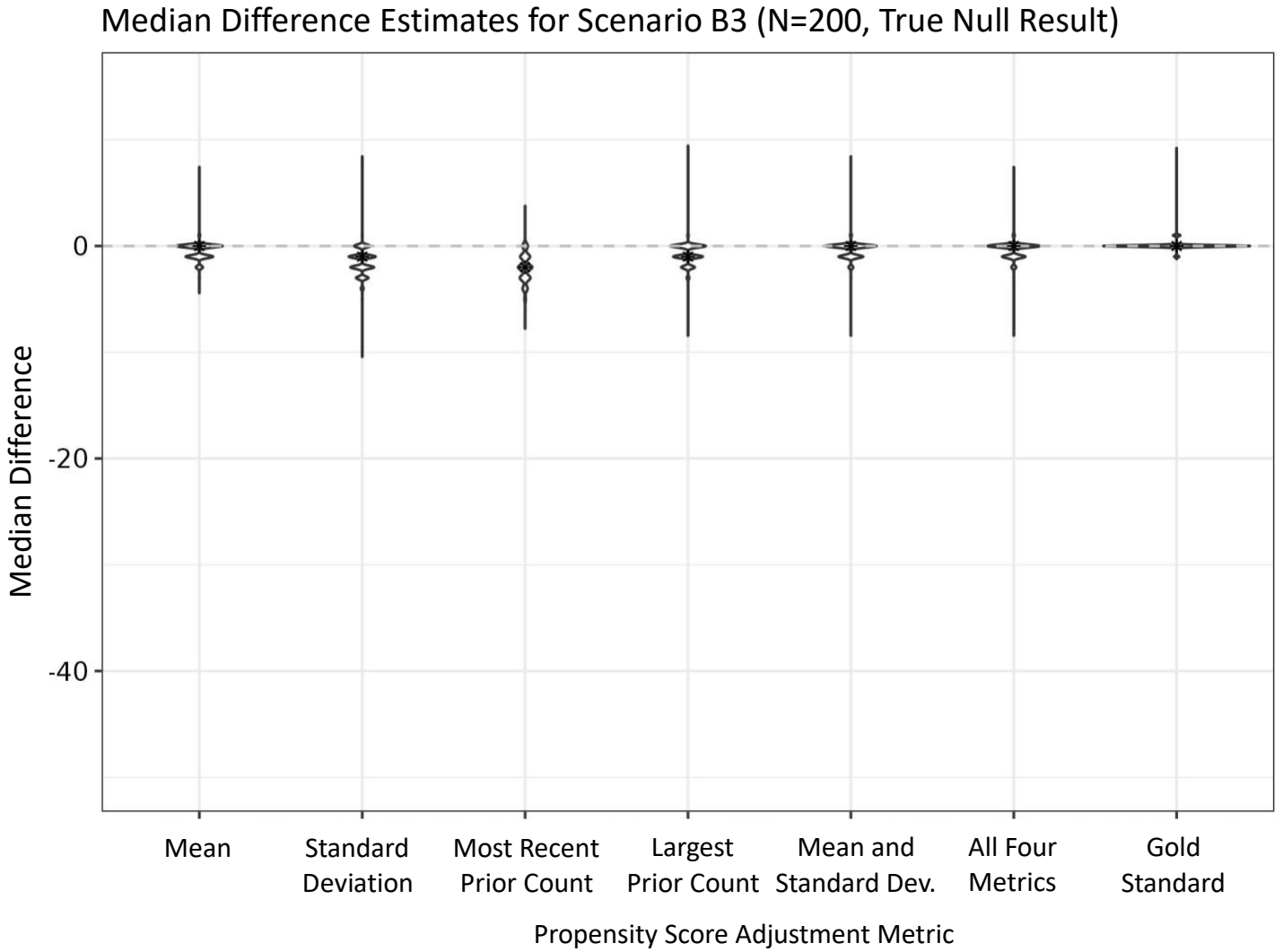
Figures Depicting the Simulation Results

Supplemental Figure 3. Violin plot depicting the adjusted differences in median platelet count between treatment groups for scenario B1, where RTM is weakly differential (0.6/0.4 probability of treatment/standard-of-care in the severe ITP group), and the platelet distributions differ disparately by underlying immune thrombocytopenia (ITP) severity (i.e., μ=100 and σ=50 for less-severe ITP versus μ=40 and σ=15 for more-severe ITP). The true change in median platelet count is null, and the initial sample size is n=200.



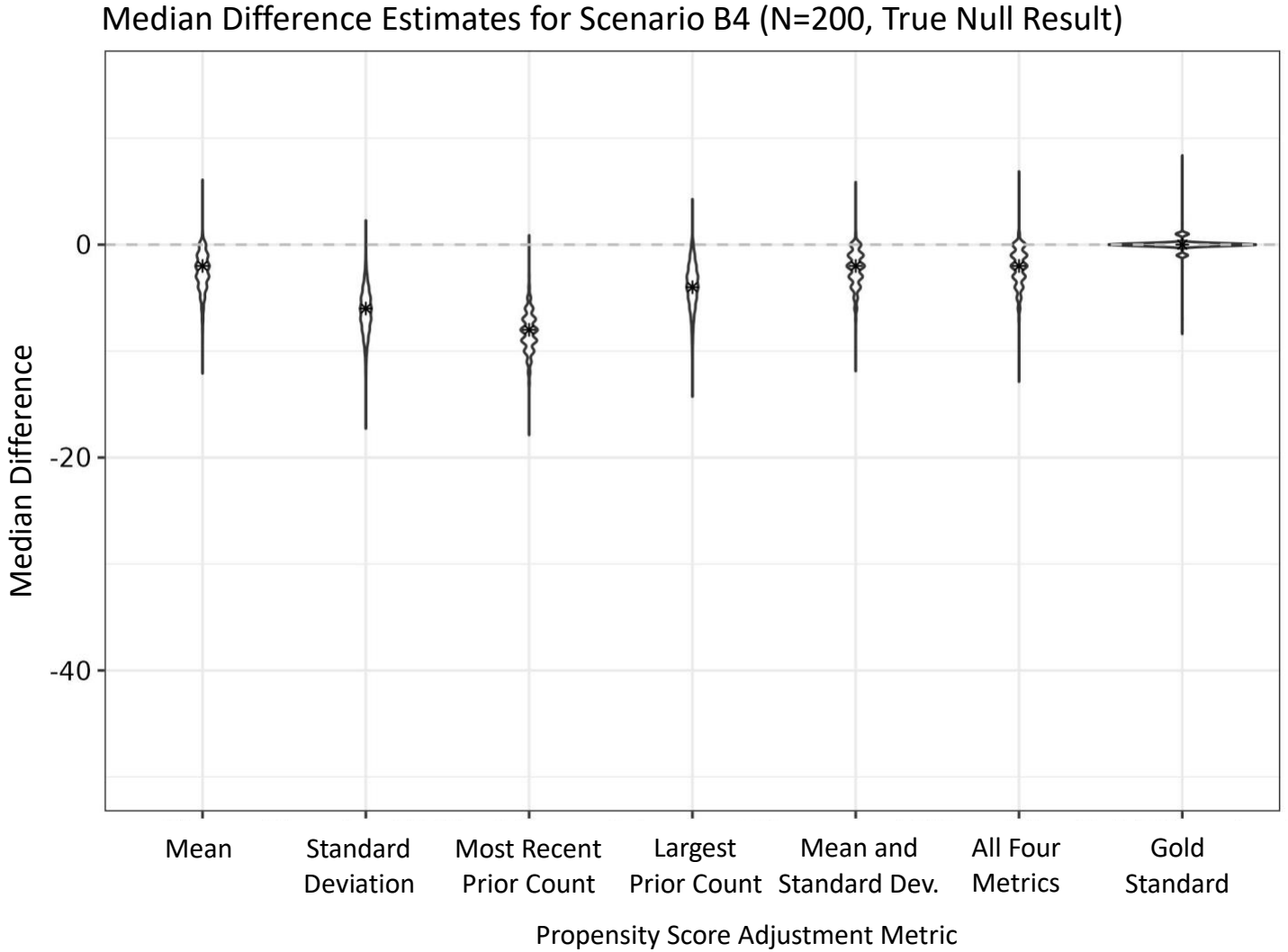
The star indicates the median of the differences between the two treatment groups' median follow-up platelet counts.

Supplemental Figure 4. Violin plot depicting the adjusted and unadjusted difference in median platelet count between treatment groups for scenario B3, where RTM is strongly differential (0.6/0.4 probability of treatment/standard-of-care in the severe ITP group), and the platelet distributions are relatively similar by underlying immune thrombocytopenia (ITP) severity (i.e., μ=55 and σ=20 for less-severe ITP versus μ=35 and σ=10 for more-severe ITP). The true change in median platelet count is null, and the initial sample size is n=200.



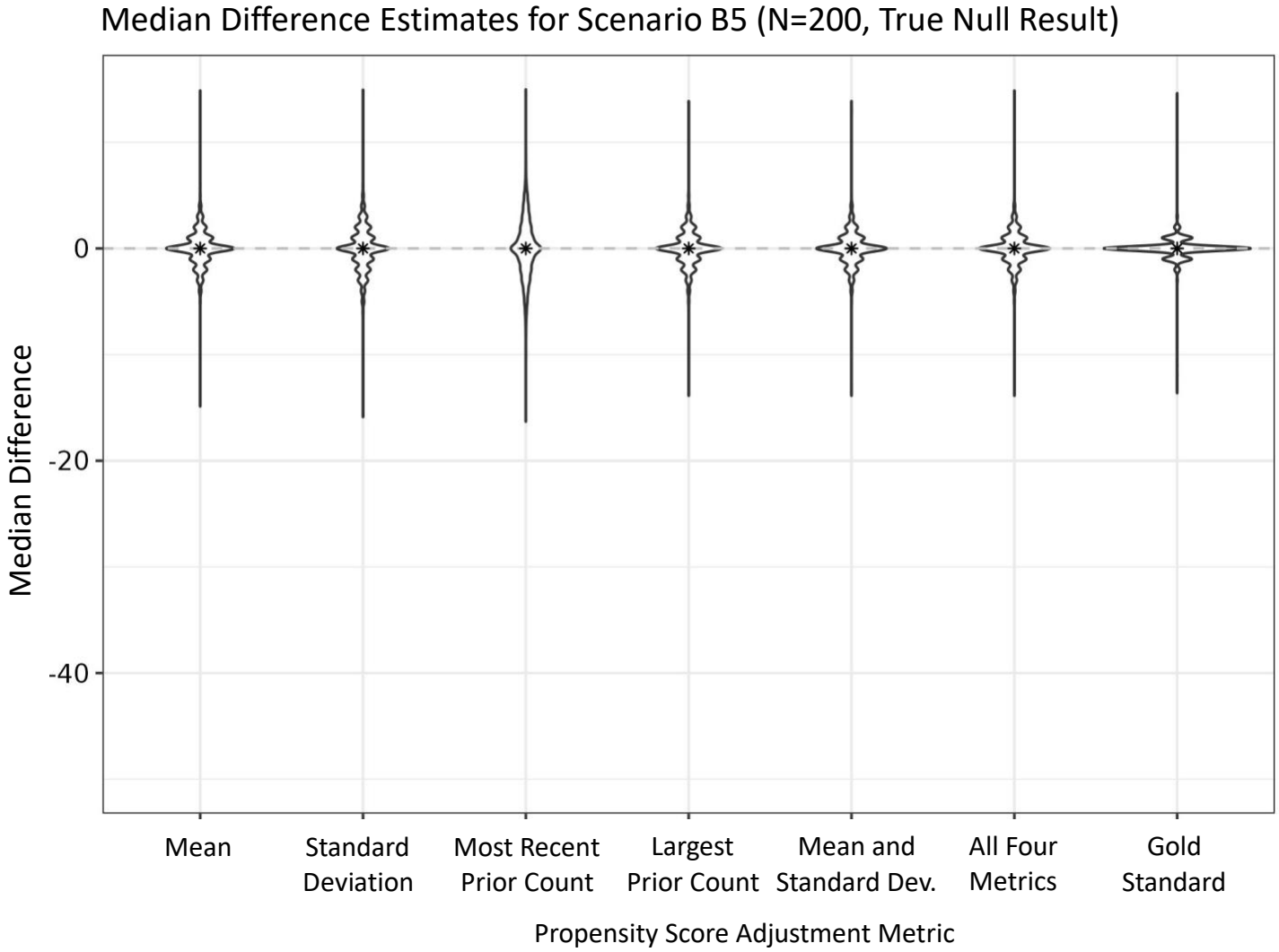
The star indicates the median of the differences between the two treatment groups' median follow-up platelet counts.

Supplemental Figure 5. Violin plot depicting the adjusted and unadjusted difference in median platelet count between treatment groups for scenario B4, where RTM is strongly differential (0.8/0.2 probability of treatment/standard-of-care in the severe ITP group), and the platelet distributions are relatively similar by underlying immune thrombocytopenia (ITP) severity (i.e., μ=55 and σ=20 for less-severe ITP versus μ=35 and σ=10 for more-severe ITP). The true change in median platelet count is null, and the initial sample size is n=200.



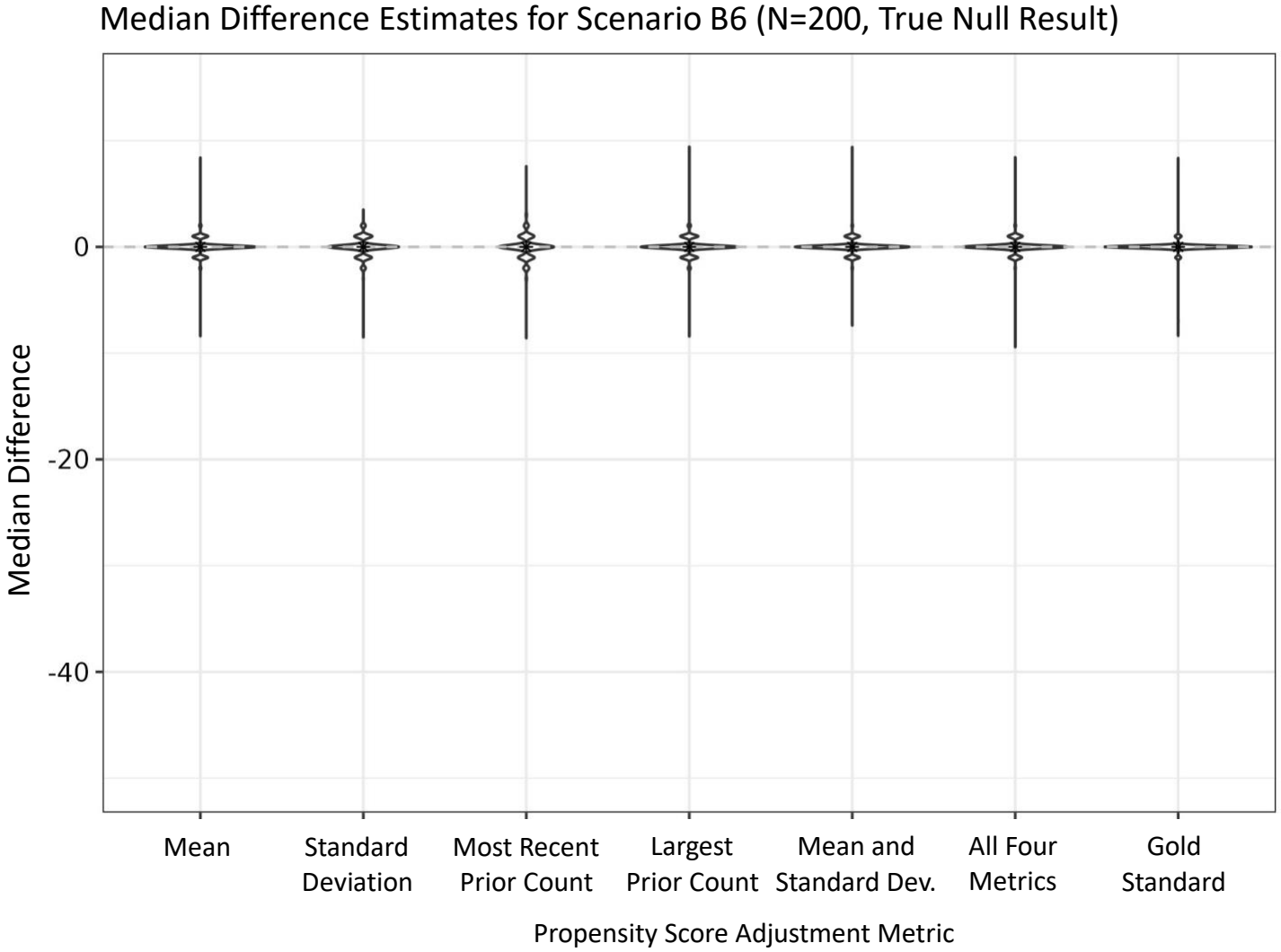
The star indicates the median of the differences between the two treatment groups' median follow-up platelet counts.

Supplemental Figure 6. Violin plot depicting the adjusted and unadjusted difference in median platelet count between treatment groups for scenario B5, where RTM is non-differential (0.5/0.5 probability of treatment/standard-of-care in the severe ITP group), and the platelet distributions differ disparately by underlying immune thrombocytopenia (ITP) severity (i.e., μ=100 and σ=50 for less-severe ITP versus μ=40 and σ=15 for more-severe ITP). The true change in median platelet count is null, and the initial sample size is n=200.



The star indicates the median of the differences between the two treatment groups' median follow-up platelet counts.

Supplemental Figure 7. Violin plot depicting the adjusted and unadjusted difference in median platelet count between treatment groups for scenario B6, where RTM is non-differential (0.5/0.5 probability of treatment/standard-of-care in the severe ITP group), and the platelet distributions are relatively similar by underlying immune thrombocytopenia (ITP) severity (i.e., μ=55 and σ=20 for less-severe ITP versus μ=35 and σ=10 for more-severe ITP). The true change in median platelet count is null, and the initial sample size is n=200.



The star indicates the median of the differences between the two treatment groups' median follow-up platelet counts.

Tables Describing the Simulation Set-Up

Supplemental Table 1. Name and description of the parameters varied across the six, core regression-to-the-mean (RTM) scenarios for each true treatment effect (i.e., null and non-null) and sample size (i.e., n=200 and n=10,000) combination for simulated immune-thrombocytopenia (ITP) patient data. The six core scenarios were applied to data with 2 possible true effects and 2 initial sample sizes, resulting in 24 scenarios in total.

Scenario	Mean and standard deviation pair (μ_i, σ_i) for platelet count distributions by ITP severity strata (i=1, 2)[a,b]	Selection probabilities for treatment/standard-of- care[c]
B1: Weakly differential RTM with platelet counts distributions that differ disparately by ITP severity	$\boldsymbol{\mu}_1$, $\boldsymbol{\sigma}_1$	0.6/0.4
B2: Strongly differential RTM with platelet count distributions that differ disparately by ITP severity	$\boldsymbol{\mu}_1$, $\boldsymbol{\sigma}_1$	0.8/0.2
B3: Weakly differential RTM with platelet count distributions that are relatively similar by ITP severity	$\boldsymbol{\mu}_2$, $\boldsymbol{\sigma}_2$	0.6/0.4
B4: Strongly differential RTM with platelet count distributions that are relatively similar by ITP severity	$\boldsymbol{\mu}_2$, $\boldsymbol{\sigma}_2$	0.8/0.2
B5: Non-differential RTM with platelet count distributions that differ disparately by ITP severity	$\boldsymbol{\mu}_1$, $\boldsymbol{\sigma}_1$	0.5/0.5
B6: Non-differential RTM with platelet count distributions that are relatively similar by ITP severity	$\boldsymbol{\mu}_2$, $\boldsymbol{\sigma}_2$	0.5/0.5

[a] $\boldsymbol{\mu}_1$, $\boldsymbol{\sigma}_1$ represents the mean and standard deviation pair for two platelet count distributions that differ disparately for the less-severe (μ=100, σ=50) versus more-severe (μ=40, σ=15) ITP strata.
[b] $\boldsymbol{\mu}_2$, $\boldsymbol{\sigma}_2$ represents the mean and standard deviation pair for two platelet count distributions that are relatively similar for the less-severe (μ=55, σ=20) versus more-severe (μ=35, σ=10) ITP strata.
[c] These selection probabilities define the degree of differential RTM. 0.8/0.2 corresponds to strongly differential RTM, 0.6/0.4 to weakly differential, and 0.5/0.5 to non-differential.

Tables Showing Descriptive Statistics of the Simulated Data

Supplemental Table 2. Descriptive summary of the patients simulated for the initial sample size of n=200 and a null true result. Counts are stratified by immune thrombocytopenia (ITP) severity (more- vs. less-severe) and treatment (treatment vs. standard-of-care [SOC]). Summary statistics are calculated over the 2,000 simulations generated for each scenario.

	More-Severe ITP				Less-Severe ITP		
Scenario	Treatment Median (IQR)	SOC Median (IQR)	Total Median (IQR)		Treatment Median (IQR)	SOC Median (IQR)	Total Median (IQR)
B1: Weakly differential RTM, Disparate platelet count distributions	60 (56, 64)	40 (36,44)	100 (95, 104)		40 (36,44)	60 (56,64)	100 (96,105)
B2: Strongly differential RTM with platelet count distributions that differ disparately ITP severity.	80 (75,85)	20 (17,23)	100 (96,105)		20 (17, 23)	80 (75, 84)	100 (95,104)
B3: Weakly differential RTM, Similar platelet count distributions	60 (56, 64)	40 (36, 44)	100 (95, 105)		40 (36, 44)	60 (55, 64)	100 (95, 105)
B4: Strongly differential RTM, Similar platelet count distributions	80 (75, 85)	20 (17, 23)	100 (95, 105)		20 (17, 23)	80 (75, 85)	100 (95, 105)
B5: Non-differential RTM, Disparate platelet count distributions	50 (46, 54)	50 (46, 54)	100 (95, 105)		50 (46, 54)	50 (46, 54)	100 (95, 105)
B6: Non-differential RTM, Similar platelet count distributions.	50 (46, 54)	50 (46, 54)	100 (95, 105)		50 (46, 54)	50 (46, 54)	100 (95, 105)

Proportions were comparable for n=10,000.

Supplemental Table 3. Descriptive summary of the simulated immune thrombocytopenia (ITP) patient platelet count data with a true null result and initial sample size of n=200, comparing the treatment and standard-of-care (SOC) groups across six regression-to-the-mean (RTM) scenarios. Platelet count means and standard deviations (SDs) were calculated for each patient and were summarized by the median of that summary measure across participants within a scenario. These data were generated over 2,000 simulations.

Scenario[a,b]	Treatment Group	Platelet Count Mean Prior to Cohort Entry[c,d] Median (Q1, Q3)	SD of Platelet Counts Prior to Cohort Entry[c,d] Median (Q1, Q3)	Platelet Count Mean After Cohort Entry[c,d] Median (Q1, Q3)	SD of Platelet Counts After Cohort Entry[c,d] Median (Q1, Q3)
B1: Weakly differential RTM, Disparate platelet count distributions	Treatment	67.76 (65.46, 69.94)	43.64 (42.22, 44.91)	64.25 (62.18, 66.36)	44.43 (43.16, 45.60)
	SOC	80.37 (78.08, 82.72)	47.62 (46.75, 48.46)	76.35 (74.23, 78.44)	49.02 (48.30, 49.67)
B2: Strongly differential RTM, Disparate platelet count distributions	Treatment	54.88 (53.02, 56.56)	34.78 (32.80, 36.59)	52.04 (50.41, 53.75)	35.25 (33.39, 36.85)
	SOC	92.93 (90.97, 94.99)	48.09 (47.34, 48.88)	88.43 (86.61, 90.02)	50.46 (50.03, 50.90)
B3: Weakly differential RTM, Similar platelet count distributions	Treatment	44.85 (44.08, 45.60)	17.11 (16.67, 17.61)	43.01 (42.30, 43.71)	17.74 (17.35, 18.15)
	SOC	49.09 (48.26, 49.88)	18.45 (18.11, 18.79)	47.01 (46.31, 47.73)	19.34 (19.09, 19.60)
B4: Strongly differential RTM, Similar platelet count distributions	Treatment	40.58 (39.96, 41.25)	14.50 (13.92, 15.07)	39.00 (38.41, 39.59)	14.91 (14.39, 15.47)
	SOC	53.30 (52.58, 53.99)	18.79 (18.45, 19.09)	51.01 (50.43, 51.60)	20.05 (19.84, 20.23)
B5: Non-differential RTM, Disparate platelet count distributions	Treatment	73.77 (71.63, 76.09)	46.04 (45.04, 47.09)	70.16 (68.13, 72.15)	47.10 (46.24, 48.01)
	SOC	73.84 (71.69, 76.17)	46.03 (44.98, 47.07)	70.18 (68.02, 72.27)	47.12 (46.17, 48.03)
B6: Non-differential RTM, Similar platelet count distributions.	Treatment	46.89 (46.13, 47.71)	17.93 (17.52, 18.32)	44.98 (44.28, 45.75)	18.68 (18.34, 18.99)
	SOC	46.99 (46.19, 47.76)	17.94 (17.52, 18.37)	45.03 (44.35, 45.74)	18.69 (18.36, 18.99)

[a] The strength of differential RTM refers to the probabilities used to select a patient's treatment based upon their predefined ITP severity strata. Strongly differential RTM corresponds to 0.8/0.2 treatment selection probabilities, weakly differential RTM to 0.6/0.4, and non-differential to 0.5/0.5.

[b] Platelet counts are derived for each patient from normal distributions with a predefined mean (μ) and standard deviation (σ). Platelet count distributions that differ disparately are defined by μ=100, σ=50 for the less-severe versus μ=40, σ=15 for the more-severe ITP strata. Platelet count distributions that are relatively similar are defined by μ=55, σ=20 for the less-severe versus μ=35, σ=10 for the more-severe ITP strata.

[c] The cohort entry event was defined as the first platelet count ≤30×10^9/L with at least 8 prior platelet counts.
[d] Statistics calculated prior to cohort entry included the 8 platelet counts measured prior to the cohort-qualifying low platelet count. Statistics estimated after cohort entry used the 23 platelet counts measured during weeks 2 through 24 after the index.

Supplemental Table 4. Descriptive summary of the simulated immune thrombocytopenia (ITP) patient platelet count data with a true non-null result and initial sample size of n=200, comparing the treatment and standard-of-care (SOC) groups across six regression-to-the-mean (RTM) scenarios. Platelet count means and standard deviations (SDs) were calculated for each patient and were summarized by the median of that summary measure across participants within a scenario. These data were generated over 2,000 simulations.

Scenario[a,b]	Treatment Group	Platelet Count Mean Prior to Cohort Entry[c,d] Median (Q1, Q3)	SD of Platelet Counts Prior to Cohort Entry[c,d] Median (Q1, Q3)	Platelet Count Mean After Cohort Entry[c,d] Median (Q1, Q3)	SD of Platelet Counts After Cohort Entry[c,d] Median (Q1, Q3)
B1: Weakly differential regression-to-the-mean, Disparate platelet count distributions	Treatment	67.76 (65.46, 69.94)	43.64 (42.22, 44.91)	114.25 (112.18, 116.36)	44.43 (43.16, 45.60)
	SOC	80.37 (78.08, 82.72)	47.62 (46.75, 48.46)	76.35 (74.23, 78.44)	49.02 (48.30, 49.67)
B2: Strongly differential RTM with platelet count distributions that differ disparately ITP severity.	Treatment	54.74 (53.04, 56.65)	34.69 (32.78, 36.60)	101.94 (100.36, 103.71)	35.13 (33.36, 36.88)
	SOC	93.22 (91.32, 95.27)	48.07 (47.35, 48.83)	88.49 (86.77, 90.22)	50.43 (49.99, 50.88)
B3: Weakly differential RTM with platelet count distributions that are relatively similar by ITP severity.	Treatment	44.83 (44.12, 45.64)	17.13 (16.67, 17.60)	93.04 (92.33, 93.72)	17.76 (17.35, 18.15)
	SOC	49.06 (48.30, 49.89)	18.48 (18.13, 18.80)	47.04 (46.30, 47.75)	19.36 (19.08, 19.63)
B4: Strongly differential regression-to-the-mean, Similar platelet count distributions	Treatment	40.54 (39.96, 41.22)	14.47 (13.92, 15.05)	88.95 (88.43, 89.56)	14.92 (14.38, 15.46)
	SOC	53.37 (52.65, 54.07)	18.78 (18.46, 19.08)	51.05 (50.45, 51.65)	20.04 (19.87, 20.25)
B5: Non-differential regression-to-the-mean, Disparate platelet count distributions	Treatment	74.06 (71.73, 76.33)	46.11 (45.04, 47.14)	120.32 (118.22, 122.38)	47.21 (46.20, 48.05)
	SOC	74.08 (71.71, 76.33)	46.11 (45.04, 47.13)	70.33 (68.12, 72.31)	47.17 (46.13, 48.07)
	Treatment	46.96 (46.13, 47.77)	17.93 (17.54, 18.31)	95.04 (94.32, 95.73)	18.69 (18.34, 19.01)

B6: Non-differential regression-to-the-mean, Similar platelet count distributions	SOC	46.97 (46.14, 47.77)	17.94 (17.56, 18.35)	45.04 (44.31, 45.73)	18.70 (18.33, 19.02)

[a] The strength of differential RTM refers to the probabilities used to select a patient's treatment based upon their predefined ITP severity strata. Strongly differential RTM corresponds to 0.8/0.2 treatment selection probabilities, weakly differential RTM to 0.6/0.4, and non-differential to 0.5/0.5.

[b] Platelet counts are derived for each patient from normal distributions with a predefined mean (μ) and standard deviation (σ). Platelet count distributions that differ disparately are defined by μ=100, σ=50 for the less-severe versus μ=40, σ=15 for the more-severe ITP strata. Platelet count distributions that are relatively similar are defined by μ=55, σ=20 for the less-severe versus μ=35, σ=10 for the more-severe ITP strata.

[c] The cohort entry event was defined as the first platelet count $\leq 30 \times 10^9$/L with at least 8 prior platelet counts.

[d] Statistics calculated prior to cohort entry included the 8 platelet counts measured prior to the cohort-qualifying low platelet count. Statistics estimated after cohort entry used the 23 platelet counts measured during weeks 2 through 24 after the index.

Supplemental Table 5. Descriptive summary of the simulated immune thrombocytopenia (ITP) patient platelet count data with a true null result and initial sample size of n=10,000, comparing the treatment and standard-of-care (SOC) groups across six regression-to-the-mean (RTM) scenarios. Platelet count means and standard deviations (SDs) were calculated for each patient and were summarized by the median of that summary measure across participants within a scenario. These data were generated over 2,000 simulations.

Scenario[a,b]	Treatment Group	Platelet Count Mean Prior to Cohort Entry[c,d] Median (Q1, Q3)	SD of Platelet Counts Prior to Cohort Entry[c,d] Median (Q1, Q3)	Platelet Count Mean After Cohort Entry[c,d] Median (Q1, Q3)	SD of Platelet Counts After Cohort Entry[c,d] Median (Q1, Q3)
B1: Weakly differential regression-to-the-mean, Disparate platelet count distributions	Treatment	67.68 (66.65, 68.62)	43.70 (43.09, 44.26)	64.21 (63.31, 65.12)	44.40 (43.87, 44.94)
	SOC	80.37 (79.34, 81.37)	47.71 (47.30, 48.08)	76.24 (75.37, 77.22)	49.04 (48.74, 49.33)
B2: Strongly differential RTM with platelet count distributions that differ disparately ITP severity.	Treatment	54.95 (54.07, 55.73)	34.87 (34.03, 35.70)	52.10 (51.37, 52.87)	35.25 (34.45, 36.07)
	SOC	93.12 (92.20, 94.01)	48.14 (47.79, 48.48)	88.36 (87.60, 89.18)	50.47 (50.28, 50.66)
B3: Weakly differential RTM with platelet count distributions that are relatively similar by ITP severity.	Treatment	44.84 (44.50, 45.17)	17.16 (16.96, 17.36)	43.02 (42.71, 43.33)	17.76 (17.59, 17.94)
	SOC	49.09 (48.72, 49.45)	18.48 (18.32, 18.64)	47.00 (46.71, 47.34)	19.36 (19.24, 19.48)
B4: Strongly differential regression-to-the-mean, Similar platelet count distributions	Treatment	40.61 (40.31, 40.89)	14.51 (14.27, 14.78)	39.01 (38.75, 39.27)	14.96 (14.73, 15.19)
	SOC	53.34 (53.02, 53.65)	18.79 (18.65, 18.93)	51.02 (50.75, 51.29)	20.06 (19.97, 20.15)
B5: Non-differential regression-to-the-mean, Disparate platelet count distributions	Treatment	74.05 (72.97, 75.04)	46.18 (45.71, 46.66)	70.25 (69.29, 71.21)	47.19 (46.75, 47.59)
	SOC	73.97 (72.97, 75.00)	46.18 (45.69, 46.64)	70.19 (69.31, 71.15)	47.13 (46.72, 47.55)
B6: Non-differential regression-to-the-mean, Similar platelet count distributions	Treatment	46.96 (46.60, 47.34)	17.96 (17.78, 18.14)	45.01 (44.69, 45.34)	18.70 (18.54, 18.84)
	SOC	46.95 (46.61, 47.32)	17.96 (17.77, 18.14)	45.01 (44.70, 45.32)	18.67 (18.53, 18.82)

[a] The strength of differential RTM refers to the probabilities used to select a patient's treatment based upon their predefined ITP severity strata. Strongly differential RTM corresponds to 0.8/0.2 treatment selection probabilities, weakly differential RTM to 0.6/0.4, and non-differential to 0.5/0.5.

[b] Platelet counts are derived for each patient from normal distributions with a predefined mean (μ) and standard deviation (σ). Platelet count distributions that differ disparately are defined by $\mu=100$, $\sigma=50$ for the less-severe versus $\mu=40$, $\sigma=15$ for the more-severe ITP strata. Platelet count distributions that are relatively similar are defined by $\mu=55$, $\sigma=20$ for the less-severe versus $\mu=35$, $\sigma=10$ for the more-severe ITP strata.

[c] The cohort entry event was defined as the first platelet count $\leq 30\times10^9$/L with at least 8 prior platelet counts.

[d] Statistics calculated prior to cohort entry included the 8 platelet counts measured prior to the cohort-qualifying low platelet count. Statistics estimated after cohort entry used the 23 platelet counts measured during weeks 2 through 24 after the index.

Supplemental Table 6. Descriptive summary of the simulated immune thrombocytopenia (ITP) patient platelet count data with a true non-null result and initial sample size of n=10,000, comparing the treatment and standard-of-care (SOC) groups across six regression-to-the-mean (RTM) scenarios. Platelet count means and standard deviations (SDs) were calculated for each patient and were summarized by the median of that summary measure across participants within a scenario. These data were generated over 2,000 simulations.

Scenario[a,b]	Treatment Group	Platelet Count Mean Prior to Cohort Entry[c,d] Median (Q1, Q3)	SD of Platelet Counts Prior to Cohort Entry[c,d] Median (Q1, Q3)	Platelet Count Mean After Cohort Entry[c,d] Median (Q1, Q3)	SD of Platelet Counts After Cohort Entry[c,d] Median (Q1, Q3)
B1: Weakly differential regression-to-the-mean, Disparate platelet count distributions	Treatment	67.68 (66.65, 68.62)	43.70 (43.09, 44.26)	114.21 (113.31, 115.12)	44.40 (43.87, 44.94)
	SOC	80.37 (79.34, 81.37)	47.71 (47.30, 48.08)	76.24 (75.37, 77.22)	49.04 (48.74, 49.33)
B2: Strongly differential RTM with platelet count distributions that differ disparately ITP severity.	Treatment	54.95 (54.07, 55.73)	34.87 (34.03, 35.70)	102.10 (101.37, 102.87)	35.25 (34.45, 36.07)
	SOC	93.12 (92.20, 94.01)	48.14 (47.79, 48.48)	88.36 (87.60, 89.18)	50.47 (50.28, 50.66)
B3: Weakly differential RTM with platelet count distributions that are relatively similar by ITP severity.	Treatment	44.84 (44.50, 45.17)	17.16 (16.96, 17.36)	93.02 (92.71, 93.33)	17.76 (17.59, 17.94)
	SOC	49.09 (48.72, 49.45)	18.48 (18.32, 18.64)	47.00 (46.71, 47.34)	19.36 (19.24, 19.48)
B4: Strongly differential regression-to-the-mean, Similar platelet count distributions	Treatment	40.61 (40.31, 40.89)	14.51 (14.27, 14.78)	89.01 (88.75, 89.27)	14.96 (14.73, 15.19)
	SOC	53.34 (53.02, 53.65)	18.79 (18.65, 18.93)	51.02 (50.75, 51.29)	20.06 (19.97, 20.15)
B5: Non-differential regression-to-the-mean, Disparate platelet count distributions	Treatment	74.05 (72.97, 75.04)	46.18 (45.71, 46.66)	120.25 (119.29, 121.21)	47.19 (46.75, 47.59)
	SOC	73.97 (72.97, 75.00)	46.18 (45.69, 46.64)	70.19 (69.31, 71.15)	47.13 (46.72, 47.55)
B6: Non-differential regression-to-the-mean, Similar platelet count distributions	Treatment	46.96 (46.60, 47.34)	17.96 (17.78, 18.14)	95.01 (94.69, 95.34)	18.70 (18.54, 18.84)
	SOC	46.95 (46.61, 47.32)	17.96 (17.77, 18.14)	45.01 (44.70, 45.32)	18.67 (18.53, 18.82)

[a] The strength of differential RTM refers to the probabilities used to select a patient's treatment based upon their predefined ITP severity strata. Strongly differential RTM corresponds to 0.8/0.2 treatment selection probabilities, weakly differential RTM to 0.6/0.4, and non-differential to 0.5/0.5.

[b] Platelet counts are derived for each patient from normal distributions with a predefined mean (μ) and standard deviation (σ). Platelet count distributions that differ disparately are defined by $\mu=100$, $\sigma=50$ for the less-severe versus $\mu=40$, $\sigma=15$ for the more-severe ITP strata. Platelet count distributions that are relatively similar are defined by $\mu=55$, $\sigma=20$ for the less-severe versus $\mu=35$, $\sigma=10$ for the more-severe ITP strata.

[c] The cohort entry event was defined as the first platelet count $\leq 30\times10^9$/L with at least 8 prior platelet counts.

[d] Statistics calculated prior to cohort entry included the 8 platelet counts measured prior to the cohort-qualifying low platelet count. Statistics estimated after cohort entry used the 23 platelet counts measured during weeks 2 through 24 after the index.

Tables Displaying Simulation Performance Measures

Supplemental Table 7. Simulation performance measures for the difference in median platelet count over the two treatment groups across all the scenarios with n=200 and a true non-null treatment effect. Measures were calculated over 2,000 simulated cohorts for each scenario.

Scenario[a,b]	Adjustment Metric for Underlying ITP Severity	Bias (95% confidence interval)	Percent Change in Absolute Bias (%)	Empirical Standard Error	Mean Square Error
B1: Weakly differential regression-to-the-mean, Disparate platelet count distributions	(1) No Adjustment	-7.47 (-10.58, -4.36)	REF	70.97	5089.83
	(2) Platelet count mean prior to cohort entry	-1.64 (-1.73, -1.55)	-78%	2.16	7.36
	(3) Platelet count standard deviation prior to cohort entry	-3.05 (-3.17, -2.93)	-59%	2.73	16.76
	(4) Difference between most recent prior platelet count and cohort entry event	-5.75 (-5.91, -5.59)	-23%	3.76	47.18
	(5) Difference between largest prior platelet count and cohort entry event	-1.75 (-1.85, -1.65)	-77%	2.21	7.93
	(6) Platelet count mean and standard deviation prior to cohort entry	-1.29 (-1.38, -1.20)	-83%	2.01	5.71
	(7) All summary measures calculated prior to cohort entry	-1.20 (-1.28, -1.12)	-84%	1.91	5.10
	(8) Gold standard	0 (-0.08, 0.08)	-100%	1.83	3.35
B2: Strongly differential regression-to-the-mean, Disparate platelet count distributions	(1) No Adjustment	-33.05 (-36.41, -29.69)	REF	76.61	6959.15
	(2) Platelet count mean prior to cohort entry	-6.70 (-6.90, -6.50)	-80%	4.50	65.16
	(3) Platelet count standard deviation prior to cohort entry	-12.98 (-13.26, -12.70)	-61%	6.44	210.03
	(4) Difference between most recent prior platelet count and cohort entry event	-23.60 (-23.92, -23.28)	-29%	7.22	608.97
	(5) Difference between largest prior platelet count and cohort entry event	-7.25 (-7.46, -7.04)	-78%	4.85	76.05
	(6) Platelet count mean and standard deviation prior to cohort entry	-5.51 (-5.68, -5.34)	-83%	3.90	45.54
	(7) All summary measures calculated prior to cohort entry	-5.19 (-5.37, -5.01)	-84%	4.15	44.14
	(8) Gold standard	-0.02	-100%	1.94	3.75

Scenario[a,b]	Adjustment Metric for Underlying ITP Severity	Bias (95% confidence interval)	Percent Change in Absolute Bias (%)	Empirical Standard Error	Mean Square Error
		(-0.11, 0.07)			
B3: Weakly differential regression-to-the-mean, Similar platelet count distributions	(1) No Adjustment	-3.30 (-4.53, -2.07)	REF	28.13	801.93
	(2) Platelet count mean prior to cohort entry	-0.87 (-0.91, -0.83)	-74%	0.95	1.65
	(3) Platelet count standard deviation prior to cohort entry	-1.99 (-2.05, -1.93)	-40%	1.26	5.56
	(4) Difference between most recent prior platelet count and cohort entry event	-2.66 (-2.72, -2.60)	-19%	1.34	8.87
	(5) Difference between largest prior platelet count and cohort entry event	-1.18 (-1.23, -1.13)	-64%	1.03	2.46
	(6) Platelet count mean and standard deviation prior to cohort entry	-0.75 (-0.79, -0.71)	-77%	0.96	1.48
	(7) All summary measures calculated prior to cohort entry	-0.71 (-0.75, -0.67)	-78%	0.92	1.34
	(8) Gold standard	-0.02 (-0.05, 0.01)	-99%	0.61	0.37
B4: Strongly differential regression-to-the-mean, Similar platelet count distributions	(1) No Adjustment	-13.09 (-14.38, -11.80)	REF	29.47	1039.26
	(2) Platelet count mean prior to cohort entry	-3.14 (-3.23, -3.05)	-76%	1.99	13.81
	(3) Platelet count standard deviation prior to cohort entry	-7.02 (-7.12, -6.92)	-46%	2.20	54.1
	(4) Difference between most recent prior platelet count and cohort entry event	-8.79 (-8.87, -8.71)	-33%	1.85	80.63
	(5) Difference between largest prior platelet count and cohort entry event	-4.54 (-4.64, -4.44)	-65%	2.21	25.45
	(6) Platelet count mean and standard deviation prior to cohort entry	-2.85 (-2.93, -2.77)	-78%	1.93	11.86
	(7) All summary measures calculated prior to cohort entry	-2.71 (-2.80, -2.62)	-79%	2.01	11.39
	(8) Gold standard	-0.03 (-0.07, 0.01)	-100%	0.84	0.71

Scenario[a,b]	Adjustment Metric for Underlying ITP Severity	Bias (95% confidence interval)	Percent Change in Absolute Bias (%)	Empirical Standard Error	Mean Square Error
B5: Non-differential regression-to-the-mean, Disparate platelet count distributions	(1) No Adjustment	-0.31 (-3.36, 2.74)	REF	69.57	4837.68
	(2) Platelet count mean prior to cohort entry	0.02 (-0.08, 0.12)	-94%	2.24	5.01
	(3) Platelet count standard deviation prior to cohort entry	0.04 (-0.08, 0.16)	-87%	2.68	7.19
	(4) Difference between most recent prior platelet count and cohort entry event	0.05 (-0.09, 0.19)	-84%	3.30	10.91
	(5) Difference between largest prior platelet count and cohort entry event	0.03 (-0.07, 0.13)	-90%	2.34	5.48
	(6) Platelet count mean and standard deviation prior to cohort entry	0.03 (-0.06, 0.12)	-90%	2.06	4.23
	(7) All summary measures calculated prior to cohort entry	0.05 (-0.04, 0.14)	-84%	1.95	3.82
	(8) Gold standard	0.03 (-0.03, 0.09)	-90%	1.34	1.78
B6: Non-differential regression-to-the-mean, Similar platelet count distributions	(1) No Adjustment	-0.06 (-1.29, 1.17)	REF	27.98	782.46
	(2) Platelet count mean prior to cohort entry	-0.02 (-0.06, 0.02)	-67%	0.97	0.93
	(3) Platelet count standard deviation prior to cohort entry	0.00 (-0.05, 0.05)	-100%	1.22	1.49
	(4) Difference between most recent prior platelet count and cohort entry event	0.00 (-0.06, 0.06)	-100%	1.41	2.00
	(5) Difference between largest prior platelet count and cohort entry event	0.00 (-0.05, 0.05)	-100%	1.04	1.08
	(6) Platelet count mean and standard deviation prior to cohort entry	-0.01 (-0.05, 0.03)	-83%	0.91	0.83
	(7) All summary measures calculated prior to cohort entry	0.01 (-0.03, 0.05)	-83%	0.88	0.77
	(8) Gold standard	-0.03 (-0.06, 0.00)	-50%	0.69	0.48

[a] The strength of differential RTM refers to the probabilities used to select a patient's treatment based upon their predefined ITP severity strata. Strongly differential RTM corresponds to 0.8/0.2 treatment selection probabilities, weakly differential RTM to 0.6/0.4, and non-differential to 0.5/0.5.

[b] Platelet counts are derived for each patient from normal distributions with a predefined mean (μ) and standard deviation (σ). Platelet count distributions that differ disparately are defined by $\mu=100$, $\sigma=50$ for the less-severe versus $\mu=40$, $\sigma=15$ for the more-severe ITP strata. Platelet count distributions that are relatively similar are defined by $\mu=55$, $\sigma=20$ for the less-severe versus $\mu=35$, $\sigma=10$ for the more-severe ITP strata.

Supplemental Table 8. Simulation performance measures for the difference in median platelet count over the two treatment groups across all the scenarios with n=10,000 and a true null treatment effect. Measures were calculated over 2,000 simulated cohorts for each scenario.

Scenario[a,b]	Adjustment Metric for Underlying ITP Severity	Bias (95% confidence interval)	Percent Change in Absolute Bias (%)	Empirical Standard Error	Mean Square Error
B1: Weakly differential regression-to-the-mean, Disparate platelet count distributions	(1) No Adjustment	-8.86 (-12.03, -5.69)	REF	72.26	5296.94
	(2) Platelet count mean prior to cohort entry	-1.47 (-1.52, -1.42)	-83%	1.11	3.37
	(3) Platelet count standard deviation prior to cohort entry	-2.95 (-3.01, -2.89)	-67%	1.33	10.48
	(4) Difference between most recent prior platelet count and cohort entry event	-5.59 (-5.66, -5.52)	-37%	1.54	33.62
	(5) Difference between largest prior platelet count and cohort entry event	-1.65 (-1.7, -1.60)	-81%	1.15	4.05
	(6) Platelet count mean and standard deviation prior to cohort entry	-1.20 (-1.24, -1.16)	-86%	0.90	2.25
	(7) All summary measures calculated prior to cohort entry	-1.19 (-1.24, -1.14)	-87%	1.15	2.73
	(8) Gold standard	0.01 (-0.02, 0.04)	-100%	0.71	0.51
B2: Strongly differential regression-to-the-mean, Disparate platelet count distributions	(1) No Adjustment	-26.59 (-29.98, -23.2)	REF	77.24	6669.52
	(2) Platelet count mean prior to cohort entry	-6.24 (-6.32, -6.16)	-77%	1.87	42.49
	(3) Platelet count standard deviation prior to cohort entry	-12.55 (-12.67, -12.43)	-53%	2.71	164.97
	(4) Difference between most recent prior platelet count and cohort entry event	-23.53 (-23.67, -23.39)	-12%	3.24	564.14
	(5) Difference between largest prior platelet count and cohort entry event	-6.74 (-6.82, -6.66)	-75%	1.88	48.93
	(6) Platelet count mean and standard deviation prior to cohort entry	-5.21 (-5.28, -5.14)	-80%	1.61	29.73
	(7) All summary measures calculated prior to cohort entry	-5.05 (-5.13, -4.97)	-81%	1.73	28.49
	(8) Gold standard	0.02	-100%	0.91	0.83

Scenario[a,b]	Adjustment Metric for Underlying ITP Severity	Bias (95% confidence interval)	Percent Change in Absolute Bias (%)	Empirical Standard Error	Mean Square Error
		(-0.02, 0.06)			
B3: Weakly differential regression-to-the-mean, Similar platelet count distributions	(1) No Adjustment	-3.31 (-4.56, -2.06)	REF	28.59	828.01
	(2) Platelet count mean prior to cohort entry	-0.83 (-0.85, -0.81)	-75%	0.55	0.99
	(3) Platelet count standard deviation prior to cohort entry	-1.96 (-1.99, -1.93)	-41%	0.61	4.21
	(4) Difference between most recent prior platelet count and cohort entry event	-2.63 (-2.66, -2.60)	-21%	0.68	7.35
	(5) Difference between largest prior platelet count and cohort entry event	-1.18 (-1.21, -1.15)	-64%	0.62	1.76
	(6) Platelet count mean and standard deviation prior to cohort entry	-0.73 (-0.76, -0.70)	-78%	0.68	1.00
	(7) All summary measures calculated prior to cohort entry	-0.72 (-0.74, -0.70)	-78%	0.57	0.84
	(8) Gold standard	0.00 (-0.03, 0.03)	-100%	0.59	0.35
B4: Strongly differential regression-to-the-mean, Similar platelet count distributions	(1) No Adjustment	-10.75 (-12.11, -9.39)	REF	31.05	1079.24
	(2) Platelet count mean prior to cohort entry	-3.01 (-3.05, -2.97)	-72%	0.89	9.84
	(3) Platelet count standard deviation prior to cohort entry	-7.01 (-7.05, -6.97)	-35%	0.97	50.07
	(4) Difference between most recent prior platelet count and cohort entry event	-8.72 (-8.76, -8.68)	-19%	0.81	76.71
	(5) Difference between largest prior platelet count and cohort entry event	-4.44 (-4.48, -4.40)	-59%	0.96	20.64
	(6) Platelet count mean and standard deviation prior to cohort entry	-2.76 (-2.80, -2.72)	-74%	0.88	8.40
	(7) All summary measures calculated prior to cohort entry	-2.72 (-2.76, -2.68)	-75%	0.84	8.08
	(8) Gold standard	0.00 (-0.02, 0.02)	-100%	0.36	0.13

Scenario[a,b]	Adjustment Metric for Underlying ITP Severity	Bias (95% confidence interval)	Percent Change in Absolute Bias (%)	Empirical Standard Error	Mean Square Error
B5: Non-differential regression-to-the-mean, Disparate platelet count distributions	(1) No Adjustment	-2.48 (-5.66, 0.70)	REF	72.53	5264.39
	(2) Platelet count mean prior to cohort entry	0.01 (-0.04, 0.06)	-100%	1.20	1.44
	(3) Platelet count standard deviation prior to cohort entry	-0.03 (-0.09, 0.03)	-99%	1.28	1.64
	(4) Difference between most recent prior platelet count and cohort entry event	0.03 (-0.04, 0.10)	-99%	1.54	2.37
	(5) Difference between largest prior platelet count and cohort entry event	0.00 (-0.05, 0.05)	-100%	1.03	1.06
	(6) Platelet count mean and standard deviation prior to cohort entry	0.00 (-0.04, 0.04)	-100%	1.01	1.03
	(7) All summary measures calculated prior to cohort entry	0.00 (-0.05, 0.05)	-100%	1.18	1.39
	(8) Gold standard	-0.03 (-0.06, 0.00)	-99%	0.74	0.55
B6: Non-differential regression-to-the-mean, Similar platelet count distributions	(1) No Adjustment	-0.97 (-2.24, 0.30)	REF	28.87	834.04
	(2) Platelet count mean prior to cohort entry	0.01 (-0.01, 0.03)	-99%	0.50	0.25
	(3) Platelet count standard deviation prior to cohort entry	-0.01 (-0.03, 0.01)	-99%	0.55	0.30
	(4) Difference between most recent prior platelet count and cohort entry event	0.01 (-0.02, 0.04)	-99%	0.61	0.37
	(5) Difference between largest prior platelet count and cohort entry event	0.00 (-0.02, 0.02)	-100%	0.50	0.25
	(6) Platelet count mean and standard deviation prior to cohort entry	0.03 (0.00, 0.06)	-97%	0.66	0.44
	(7) All summary measures calculated prior to cohort entry	0.01 (-0.01, 0.03)	-99%	0.49	0.24
	(8) Gold standard	-0.01 (-0.03, 0.01)	-99%	0.37	0.13

[a] The strength of differential RTM refers to the probabilities used to select a patient's treatment based upon their predefined ITP severity strata. Strongly differential RTM corresponds to 0.8/0.2 treatment selection probabilities, weakly differential RTM to 0.6/0.4, and non-differential to 0.5/0.5.

[b] Platelet counts are derived for each patient from normal distributions with a predefined mean (μ) and standard deviation (σ). Platelet count distributions that differ disparately are defined by $\mu=100$, $\sigma=50$ for the less-severe versus $\mu=40$, $\sigma=15$ for the more-severe ITP strata. Platelet count distributions that are relatively similar are defined by $\mu=55$, $\sigma=20$ for the less-severe versus $\mu=35$, $\sigma=10$ for the more-severe ITP strata.

Supplemental Table 9. Simulation performance measures for the difference in median platelet count over the two treatment groups across all the scenarios with n=10,000 and a true non-null treatment effect. Measures were calculated over 2,000 simulated cohorts for each scenario.

Scenario[a,b]	Adjustment Metric for Underlying ITP Severity	Bias (95% confidence interval)	Percent Change in Absolute Bias (%)	Empirical Standard Error	Mean Square Error
B1: Weakly differential regression-to-the-mean, Disparate platelet count distributions	(1) No Adjustment	-8.53 (-11.70, -5.36)	REF	72.41	5313.43
	(2) Platelet count mean prior to cohort entry	-1.47 (-1.52, -1.42)	-83%	1.20	3.59
	(3) Platelet count standard deviation prior to cohort entry	-2.90 (-2.98, -2.82)	-66%	1.85	11.87
	(4) Difference between most recent prior platelet count and cohort entry event	-5.60 (-5.67, -5.53)	-34%	1.53	33.70
	(5) Difference between largest prior platelet count and cohort entry event	-1.62 (-1.68, -1.56)	-81%	1.42	4.66
	(6) Platelet count mean and standard deviation prior to cohort entry	-1.20 (-1.24, -1.16)	-86%	0.89	2.22
	(7) All summary measures calculated prior to cohort entry	-1.19 (-1.24, -1.14)	-86%	1.22	2.91
	(8) Gold standard	0.03 (-0.02, 0.08)	-100%	1.16	1.34
B2: Strongly differential regression-to-the-mean, Disparate platelet count distributions	(1) No Adjustment	-26.84 (-30.22, -23.46)	REF	77.18	6673.86
	(2) Platelet count mean prior to cohort entry	-6.21 (-6.30, -6.12)	-77%	2.11	43.03
	(3) Platelet count standard deviation prior to cohort entry	-12.48 (-12.62, -12.34)	-54%	3.11	165.47
	(4) Difference between most recent prior platelet count and cohort entry event	-23.47 (-23.62, -23.32)	-13%	3.42	562.64
	(5) Difference between largest prior platelet count and cohort entry event	-6.72 (-6.81, -6.63)	-75%	2.03	49.32
	(6) Platelet count mean and standard deviation prior to cohort entry	-5.19 (-5.27, -5.11)	-81%	1.83	30.25
	(7) All summary measures calculated prior to cohort entry	-5.04 (-5.13, -4.95)	-81%	2.02	29.43
	(8) Gold standard	0.04	-100%	1.24	1.53

Scenario[a,b]	Adjustment Metric for Underlying ITP Severity	Bias (95% confidence interval)	Percent Change in Absolute Bias (%)	Empirical Standard Error	Mean Square Error
		(-0.01, 0.09)			
B3: Weakly differential regression-to-the-mean, Similar platelet count distributions	(1) No Adjustment	-3.20 (-4.49, -1.91)	REF	29.34	870.48
	(2) Platelet count mean prior to cohort entry	-0.86 (-0.88, -0.84)	-73%	0.55	1.04
	(3) Platelet count standard deviation prior to cohort entry	-1.98 (-2.01, -1.95)	-38%	0.63	4.31
	(4) Difference between most recent prior platelet count and cohort entry event	-2.65 (-2.68, -2.62)	-17%	0.64	7.46
	(5) Difference between largest prior platelet count and cohort entry event	-1.17 (-1.19, -1.15)	-63%	0.44	1.56
	(6) Platelet count mean and standard deviation prior to cohort entry	-0.73 (-0.75, -0.71)	-77%	0.51	0.80
	(7) All summary measures calculated prior to cohort entry	-0.72 (-0.74, -0.70)	-78%	0.47	0.74
	(8) Gold standard	-0.01 (-0.03, 0.01)	-100%	0.39	0.15
B4: Strongly differential regression-to-the-mean, Similar platelet count distributions	(1) No Adjustment	-13.05 (-14.36, -11.74)	REF	30.00	1069.88
	(2) Platelet count mean prior to cohort entry	-3.05 (-3.13, -2.97)	-77%	1.90	12.91
	(3) Platelet count standard deviation prior to cohort entry	-6.84 (-6.93, -6.75)	-48%	2.15	51.35
	(4) Difference between most recent prior platelet count and cohort entry event	-8.68 (-8.76, -8.60)	-33%	1.87	78.90
	(5) Difference between largest prior platelet count and cohort entry event	-4.39 (-4.49, -4.29)	-66%	2.19	24.06
	(6) Platelet count mean and standard deviation prior to cohort entry	-2.76 (-2.84, -2.68)	-79%	1.83	10.95
	(7) All summary measures calculated prior to cohort entry	-2.59 (-2.67, -2.51)	-80%	1.93	10.42
	(8) Gold standard	-0.02 (-0.06, 0.02)	-100%	0.87	0.76

Scenario[a,b]	Adjustment Metric for Underlying ITP Severity	Bias (95% confidence interval)	Percent Change in Absolute Bias (%)	Empirical Standard Error	Mean Square Error
B5: Non-differential regression-to-the-mean, Disparate platelet count distributions	(1) No Adjustment	-2.38 (-5.57, 0.81)	REF	72.68	5285.40
	(2) Platelet count mean prior to cohort entry	0.03 (-0.04, 0.10)	-99%	1.68	2.81
	(3) Platelet count standard deviation prior to cohort entry	-0.04 (-0.09, 0.01)	-98%	1.22	1.50
	(4) Difference between most recent prior platelet count and cohort entry event	0.03 (-0.04, 0.10)	-99%	1.70	2.88
	(5) Difference between largest prior platelet count and cohort entry event	-0.02 (-0.06, 0.02)	-99%	0.90	0.81
	(6) Platelet count mean and standard deviation prior to cohort entry	0.01 (-0.05, 0.07)	-100%	1.32	1.74
	(7) All summary measures calculated prior to cohort entry	-0.02 (-0.07, 0.03)	-99%	1.21	1.46
	(8) Gold standard	0.00 (-0.05, 0.05)	-100%	1.17	1.38
B6: Non-differential regression-to-the-mean, Similar platelet count distributions	(1) No Adjustment	-0.93 (-2.20, 0.34)	REF	28.94	837.99
	(2) Platelet count mean prior to cohort entry	-0.01 (-0.03, 0.01)	-99%	0.39	0.15
	(3) Platelet count standard deviation prior to cohort entry	-0.02 (-0.04, 0.00)	-98%	0.56	0.31
	(4) Difference between most recent prior platelet count and cohort entry event	0.00 (-0.03, 0.03)	-100%	0.62	0.38
	(5) Difference between largest prior platelet count and cohort entry event	-0.01 (-0.03, 0.01)	-99%	0.46	0.21
	(6) Platelet count mean and standard deviation prior to cohort entry	-0.01 (-0.03, 0.01)	-99%	0.41	0.17
	(7) All summary measures calculated prior to cohort entry	-0.01 (-0.03, 0.01)	-99%	0.37	0.14
	(8) Gold standard	-0.02 (-0.04, 0.00)	-98%	0.36	0.13

[a] The strength of differential RTM refers to the probabilities used to select a patient's treatment based upon their predefined ITP severity strata. Strongly differential RTM corresponds to 0.8/0.2 treatment selection probabilities, weakly differential RTM to 0.6/0.4, and non-differential to 0.5/0.5.

[b] Platelet counts are derived for each patient from normal distributions with a predefined mean (μ) and standard deviation (σ). Platelet count distributions that differ disparately are defined by μ=100, σ=50 for the less-severe versus μ=40, σ=15 for the more-severe ITP strata. Platelet count distributions that are relatively similar are defined by μ=55, σ=20 for the less-severe versus μ=35, σ=10 for the more-severe ITP strata.