Adaptive Design Report for the Post-Operative Nausea and Vomiting (PONV) Prophylaxis Domain

Version 2.0

UPMC REMAP: Perioperative Medicine (Periop)

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ABBREVIATIONS

ADR: Adaptive Design Report
HFD: Hospital Free Days
ITT: Intention to Treat
MCMC: Markov Chain Monte Carlo
mITT: Modified Intention to Treat
OR: Odds Ratio
PP: Per Protocol
RAR: Response Adaptive Randomization

1. DOCUMENT VERSION

The version of the Adaptive Design Report is in this document's header and on the cover page.

1.1. Version history

Version 1: 3 April 2023
Version 2: 14 June 2023

- Surgery type effects and time era effects definitions are updated to align with the Core ADR.
- Changed analysis population to be modified intention to treat. This will include all patients who have undergone surgery and analyzing them by the interventions to which they were randomized.
- Clarified that time adjustments will not be included in this model.

2. INTRODUCTION

This ADR describes the domain-specific design including statistical modeling, statistical triggers, and domain operating characteristics for one domain within the UPMC REMAP Periop.

2.1. Interventions

There are two interventions included in this domain:

- A1: Optimal prophylaxis
- A2: Supraoptimal prophylaxis

2.2. Primary Endpoint

The primary endpoint for this domain is hospital free days (HFD) at 30 days after the surgical encounter. Statistical triggers will be evaluated on HFD at each adaptive analysis for this domain.

2.3. Domain-Specific Key Secondary Endpoint

In addition to the platform primary endpoint, the domain-specific key secondary endpoint is post-operative nausea and vomiting (PONV). PONV is a dichotomous endpoint for whether the patient has 1 or more doses of antiemetic medications within 24 hours of completion of surgery. Statistical triggers will be evaluated on PONV at each adaptive analysis for this domain.

3. PRIMARY STATISTICAL ANALYSIS MODEL

3.1. Domain-specific Additive Treatment Effects

The table below summarizes the additive effects contributed to the primary HFD analysis model by the PONV domain. Intervention effects are estimated for A2 relative to intervention A1 which is fixed to 0. The A2 intervention treatment effect is estimated with a standard normal prior. An effect is also estimated for randomization to any intervention within the domain.

Summary of Domain Additive Effects in HFD Model				
Factor	**Level**	**Parameter**	**Prior**	**Notes**
Intervention	A1	θ_{B1}	0	Fixed to zero (reference group).
	A2	θ_{B2}	N(0, 1)	Treatment effects estimated relative to A1.
PONV Domain Randomization	Randomized within domain	β_A	N(0, 1)	Indicator defined as: - 0 if not randomized within PONV domain - 1 if randomized within PONV domain (Assignment to A1 or A2)

4. KEY SECONDARY STATISTICAL ANALYSIS MODEL

This section describes the statistical modeling applied for the domain-specific key secondary endpoint, PONV. The analysis model for PONV is a Bayesian logistic regression model. Let $PONV_i$ denote the PONV outcome for participant i. For each participant i, it is assumed that

$$PONV_i \sim Bernoulli(q_i),$$

Where q_i is the probability of PONV for participant i. The Bayesian logistic regression model specification is:

$$\text{logit}(q_i) = \alpha_0 + \boldsymbol{s_i^T \alpha} + \boldsymbol{z_i^T \beta} + \boldsymbol{x_i^T \theta}, \quad (1)$$

Where $\text{logit}(q_i)$ is the log odds of q_i. The vector $\boldsymbol{s_i} = (s_{i1}, \ldots, s_{iS})$ includes indicators of the surgery type received by participant i. The variables $\boldsymbol{z_i} = (z_{i1}, \ldots, z_{ip})$ represent covariates included in the model, and the vector $\boldsymbol{x}_i = (x_{i1}, \ldots, x_{ik})$ consists of indicators of intervention assignment for each of the k interventions included in the model. If participant i was randomized to intervention t at baseline, then $x_{it} = 1$; otherwise $x_{it} = 0$. The parameter $\boldsymbol{\theta}$ is the *k*-dimensional vector of treatment effects for interventions $1, \ldots, k$.

The treatment effects, $\boldsymbol{\theta}$, are interpretable as log odds ratios for PONV. Values of $\boldsymbol{\theta}$ greater than zero indicate increased odds of PONV, and values of $\boldsymbol{\theta}$ less than zero indicate decreased odds of PONV. The reference intervention in this domain is A1 (optimal prophylaxis), so the log odds ratio for this intervention is fixed to zero. The log odds ratio is estimated for A2 relative to A1. As in the primary HFD model, a normally distributed prior with mean 0 and standard deviation 1 is specified for the log odds ratio of A2. Treatment effect summaries will also be presented in terms of the PONV odds ratio, $\exp(\boldsymbol{\theta})$, for A2 relative to A1.

The PONV model includes adjustments for the following factors: age category, sex, hospital site, baseline preoperative health class, surgery type, domain randomization status, and randomization in the Analgesia domain. No adjustment for time is included in this model. If domains are added to the platform in the future, effects for randomization in the new domain(s) may be added to the PONV model and would be specified in the Current State of the Statistical Models document at that time. For the factors that also appear in the primary HFD model, the same priors will be used in the PONV model as specified in the HFD model (described in Section 3 of the Core ADR). For other model parameters, the prior specification is provided in the sections below.

4.1. Intercept Term Prior

The intercept term, α_0, determines the probability of PONV in the reference group of participants with all zero-valued covariates. We specify a uniform Beta(1,1) prior on the probability of PONV in the reference group, and the prior for α_0 is a logit (log-odds) transformation of the uniform prior.

4.2. Surgery Type Effects

A covariate for surgery type will be included in the PONV model. The referent surgery type will be the category relating to “abdominal complex” surgeries. Effects will be estimated for each other

surgery type relative to the reference surgery type. Independent standard normal priors are used for each surgery type effect.

4.3. Domain Randomization Effects

A covariate for domain randomization will be included for the PONV and Analgesia domains in the PONV model. Independent standard normal priors will be used for each domain randomization effect. If other domains are added to the PONV model in the future, an effect for randomization to the new domain would be added to the model with an independent normal prior distribution.

4.4. Other Domain Intervention Effects

The PONV model will adjust for randomization assignment within the Analgesia domain. The B1 intervention will be the reference intervention, and log odds ratios will be estimated for each remaining intervention relative to B1. Independent standard normal priors will be used for each intervention effect.

If other domains are added to the PONV model in the future, the default prior for intervention effects would be a standard normal prior. Modeling details for new domains, including deviations from this default prior, will be specified in the Current State of the Statistical Models document.

4.5. Analysis Population

The PONV model will be analyzed in the PONV modified ITT population. This population consists of all participants that are randomized to at least one intervention within the PONV Prophylaxis or Analgesia domains and have undergone surgery. If new domains are added the PONV model, the PONV mITT population may be expanded to include additional domains. Any modification of the PONV mITT population would be specified in the Current State of the Statistical Models document.

5. DOMAIN DESIGN

5.1. Adaptive Analyses

At each platform adaptive analysis, the statistical triggers prespecified for this domain will be evaluated in the primary HFD model and the domain-specific PONV model.

5.2. Allocation

Participants will be randomized with fixed, equal randomization (1:1) between the two interventions within this domain. Participants must be eligible for the domain and both interventions to be randomized within the domain.

6. STATISTICAL TRIGGERS

6.1. Intervention Superiority

This domain includes a statistical trigger of superiority for each intervention within the domain. If, at any interim analysis, one intervention has a posterior probability of 99% or greater that it is optimal, then that intervention would be declared superior, and the comparator arm would be declared inferior. Upon meeting the statistical trigger, the inferior arm would be dropped, and results would be publicly disclosed. This statistical trigger is applied to both HFD and PONV endpoints, and superiority would be declared upon meeting the trigger for either of the two endpoints.

6.2. Equivalence

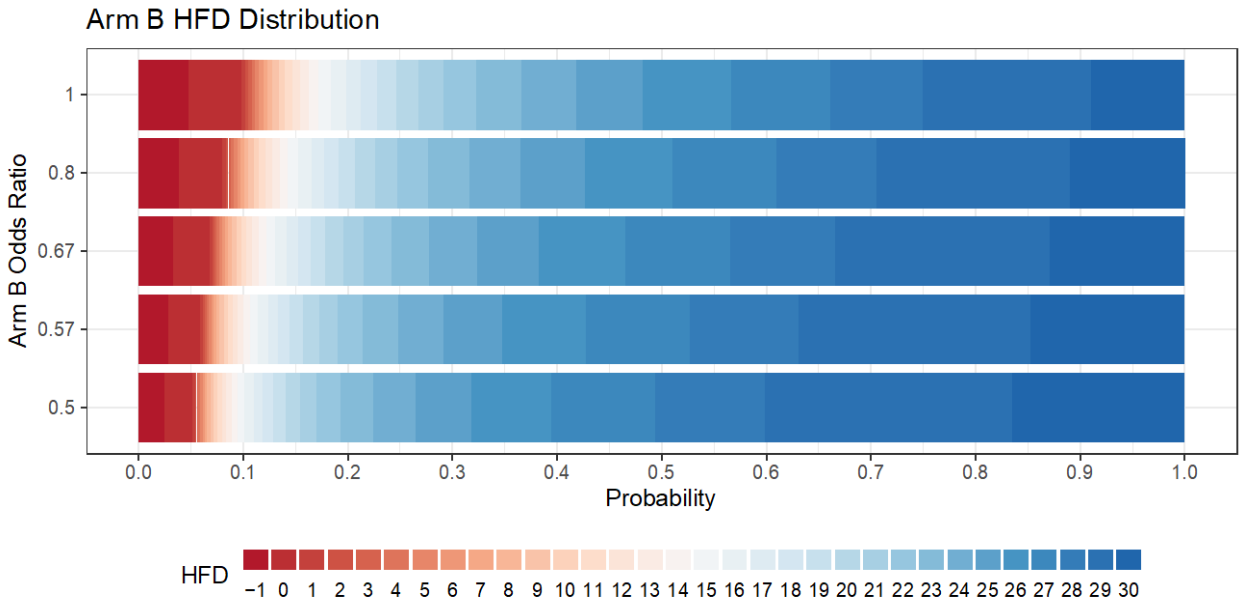
This domain includes a statistical trigger for equivalence of the two interventions in the domain. For both HFD and PONV endpoints, the equivalence trigger is defined as a greater than 90% probability that the odds ratio for A2 relative to A1 falls between 1/1.2 (0.83) and 1.2. Equivalence will be declared upon meeting the statistical trigger for either the HFD or PONV endpoints.

7. DOMAIN OPERATING CHARACTERISTICS

To characterize the performance of the design, we simulate the domain under different scenarios and summarize the outcome across thousands of simulated trials. In the sections below, we describe the assumptions used to generate the virtual patient data. Additionally, we summarize the probability of reaching platform conclusions based on the HFD and PONV endpoints. These simulations are restricted to the PONV domain of the platform. We present simulations for a general arm A versus arm B since the same set of statistical triggers apply to both interventions.

7.1. HFD Scenarios

The assumptions for the HFD distribution are based on existing data for elective surgery patients within the UPMC system. The HFD distribution on arm A is based on the HFD outcome rates observed in the available data. A range of treatment effects are explored for arm B versus arm A. The treatment effects are HFD odds ratios (OR) for arm B versus arm A. An odds ratio of 1 indicates no difference in HFD outcomes between the two arms. Odds ratios below 1 indicate arm B reduces the odds of worse HFD outcomes compared to arm A. The figure below visualizes the HFD distribution on arm B for each treatment effect scenario.



7.2. PONV Scenarios

In existing data, the rates of PONV in elective surgery patients are approximately 10 to 20%. Simulations are performed in three scenarios assuming PONV rates of 10, 15, and 20% for arm A. For each PONV scenario, a range of treatment effects are explored for arm B versus arm A. The treatment effects are PONV odds ratios (OR) for arm B versus arm A. An odds ratio of 1 indicates no difference in PONV rates between the two arms. Odds ratios below 1 indicate arm B reduces the odds of PONV compared to arm A. The table below summarizes the PONV rate on arm B for each PONV and treatment effect scenario.

Arm A PONV rate (%)	**Arm B PONV rate (%)**				
	OR=1	***OR=0.8***	***OR=0.67***	***OR=0.57***	***OR=0.50***

10	10.0	8.2	6.9	6.0	5.3
15	15.0	12.4	10.5	9.2	8.1
20	20.0	16.7	14.3	12.5	11.1

7.3. Simulation Assumptions

No sample size maximum is specified for this domain, but the simulations assume a maximum of 5000 participants enrolled in the PONV domain. In the simulations, the quarterly adaptive analyses are approximated by analyses conducted every 500 patients with complete outcomes. Simulations are performed separately for each domain endpoint (HFD and PONV). These simulations do not incorporate missing data. Covariates are not simulated or incorporated into the statistical model in these simulations. For each simulation scenario, we simulate 5000 trials.

Each figure below summarizes the cumulative probability of meeting statistical triggers in the domain for each endpoint. The x-axis in each plot is the total number of patients enrolled into the domain, and the y-axis is the cumulative probability a trigger is met. Each green line shows the cumulative probability of declaring arm B superior to arm A at each sample size. Each red line shows the cumulative probability of declaring arm B inferior to arm A (or equivalently, arm A superior to arm B) at each sample size. Each orange line shows the cumulative probability of declaring arms A and B equivalent.

Figure 1 Cumulative Operating Characteristics for Hospital Free Days

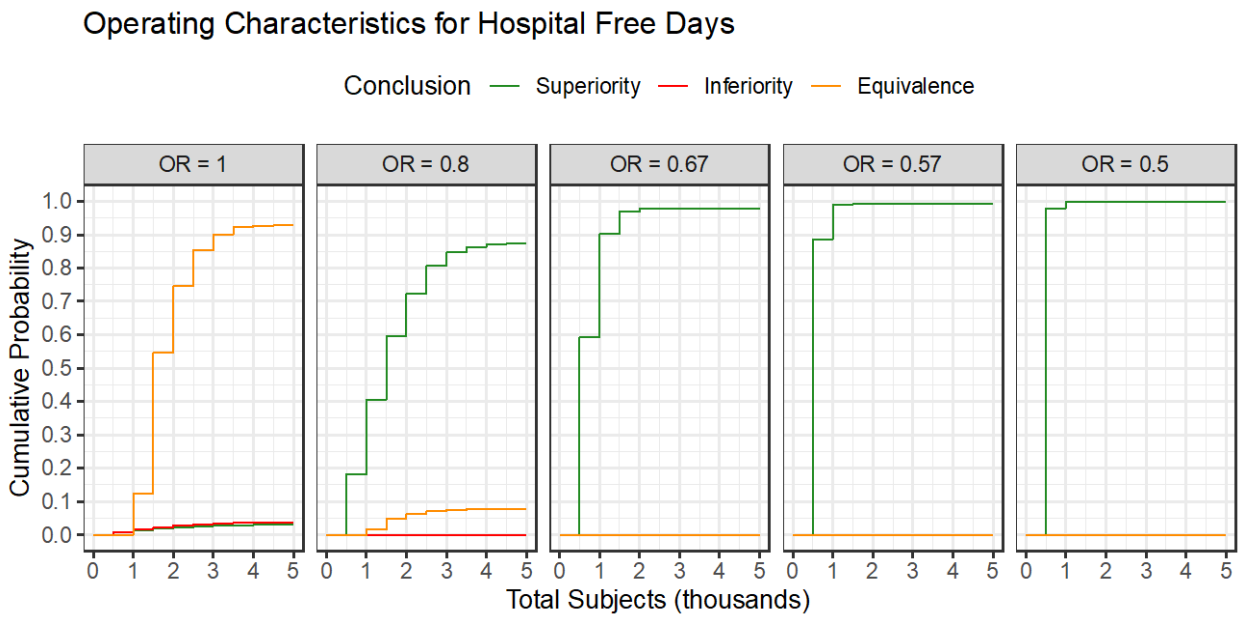


Figure 2 Cumulative Operating Characteristics with a 20% PONV Rate on Arm A

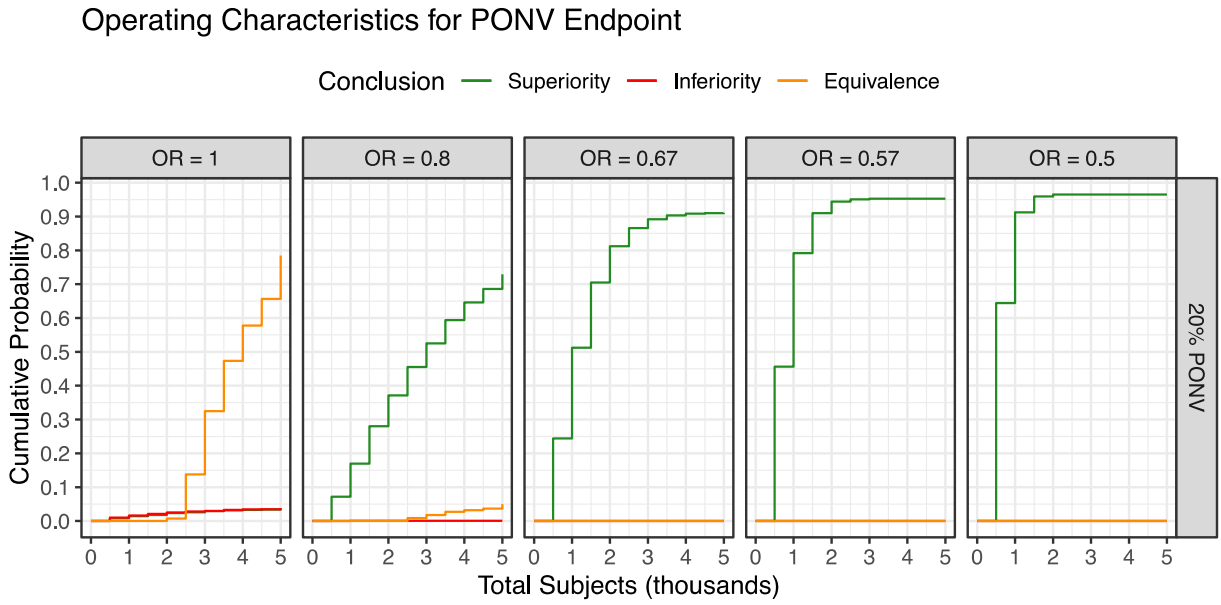


Figure 3 Cumulative Operating Characteristics with a 15% PONV Rate on Arm A

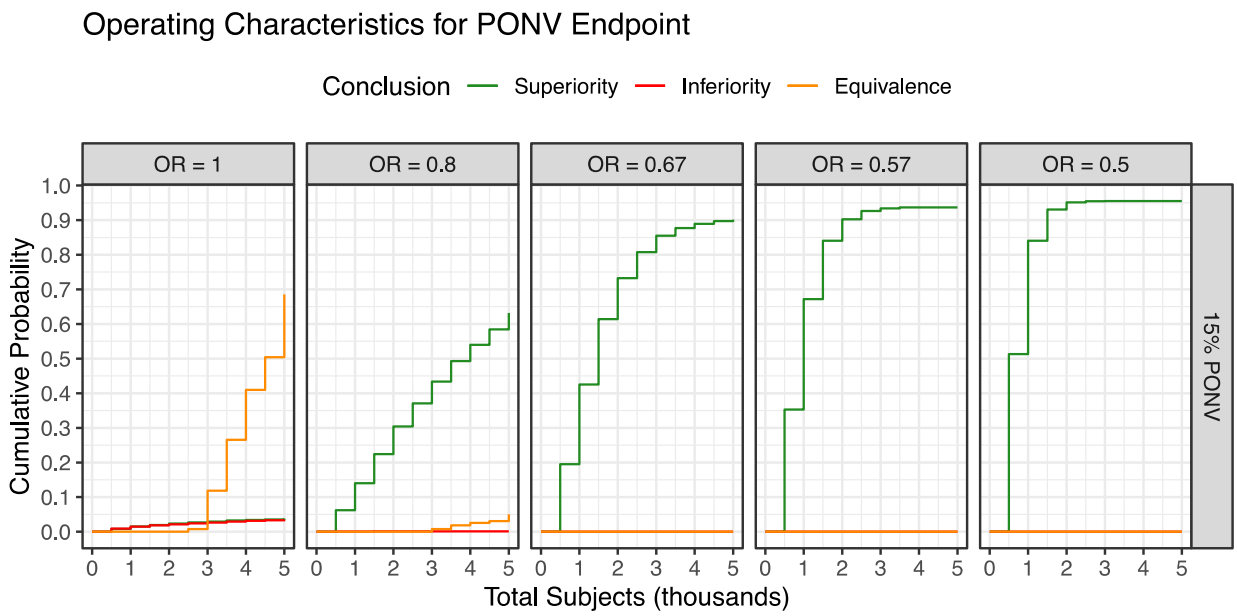


Figure 4 Cumulative Operating Characteristics with a 10% PONV Rate on Arm A