Adaptive Design Report for the Analgesia 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
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.
- Changed timing of the initiation of RAR. RAR will now begin once specific conditions are met among the single agents. These conditions are outlined in Section 6
- Statistical trigger section has been updated to reflect two levels of statistical triggers. The first level involves triggers among the single agents and the second level opens up triggers to the remaining combination agents.
- The operating characteristics for the OME endpoint have been updated to reflect the design changes described in Section 6.

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 five interventions included in this domain:

- B1: Neuraxial (intrathecal morphine)
- B2: Regional Block 1 (paravertebral)
- B3: Regional Block 2 (QL3)
- B4: Neuraxial and Regional Block 1 (IT morphine and paravertebral)
- B5: Neuraxial and Regional Block 2 (IT morphine and QL3)

Interventions B1, B2, and B3 are single agent interventions while B4 and B5 are combinations of the other interventions in the domain. Statistical triggers are defined comparing the efficacy of the single agent interventions, and comparing the efficacy of combinations relative to the component agents.

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 the total oral morphine equivalents (OME) on postoperative day 0 and 1. OME measurement is a method to compare and standardize different opioids administered to patients to account for varying strengths. OME is measured as a rate in milligrams per day and modeled as a continuous endpoint. Statistical triggers will be evaluated on OME and HFD 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 Analgesia domain. Intervention effects are estimated for B2 through B5 relative to intervention B1 which is fixed to 0. Each intervention treatment effect is estimated with independent standard normal priors. It is noted that interventions B4 and B5 are modeled as separate interventions and not as the combination of B1+B2 and B1+B3, respectively. 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	B1	θ_{B1}	0	Fixed to zero (reference group).
	B2	θ_{B2}	N(0, 1)	Treatment effects estimated relative to B1.
	B3	θ_{B3}	N(0, 1)	
	B4	θ_{B4}	N(0, 1)	
	B5	θ_{B5}	N(0, 1)	
Analgesia Domain Randomization	Randomized within domain	β_B	N(0, 1)	Indicator defined as: - 0 if not randomized within Analgesia domain

				- 1 if randomized within Analgesia domain (Assignment to B1 through B5)

4. KEY SECONDARY STATISTICAL ANALYSIS MODEL

This section describes the statistical modeling applied for the domain-specific primary endpoint, OME. The analysis model for OME is a Bayesian linear regression model.

In this model, the OME outcome is transformed based on the expectation of a non-normal distribution. In pre-existing OME data, the OME distribution is right-skewed and bounded below by 0. OME values of 0 are possible but rare in the available data. In this model, the dependent outcomes will be the log-transformation of 1 plus the OME values. The constant of 1 is added to each patient's OME value to handle the possibility of observing 0 OME.

Let OME_i denote the OME outcome for participant i. The Bayesian linear regression model specification is:

$$\begin{aligned} &\log(OME_i + 1) = \alpha_0 + \boldsymbol{s_i^T \alpha} + \boldsymbol{z_i^T \beta} + \boldsymbol{x_i^T \theta} + \epsilon_i, \\ &\epsilon_i \sim N(0, \sigma^2) \end{aligned} \tag{1}$$

The vector $\boldsymbol{s_i} = (s_{i1}, \dots, s_{iS})$ includes indicators of the surgery type received by participant i. The variables $\boldsymbol{z_i} = (z_{i1}, \dots, z_{ip})$ represent covariates included in the model, and the vector $\boldsymbol{x}_i = (x_{i1}, \dots, x_{ik})$ 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 $1, \dots, k$.

The treatment effects, $\boldsymbol{\theta}$, are interpretable as differences in mean outcomes. Values of $\boldsymbol{\theta}$ greater than zero indicate increased OME, and values of $\boldsymbol{\theta}$ less than zero indicate decreased OME. The reference intervention in this domain is B1, so the treatment effect for this intervention is fixed to zero. The treatment effects of B2 through B5 are estimated relative to B1. In this model, normally

distributed priors with mean 0 and standard deviation 2 are specified for the treatment effects relative to B1.

The OME model includes adjustments for the following: age category, sex, hospital site, time epoch, baseline preoperative health class, surgery type, opioid tolerance, domain randomization status, and randomization in the Analgesia domain. For each model parameter, the prior specification is provided in the following sections. If domains are added to the platform in the future, effects for randomization in the new domain(s) may be added to the OME model and would be specified in the Current State of the Statistical Models document at that time.

4.1. Intercept Prior

The intercept parameter, α_0, is estimated with a non-informative prior that is normally distributed prior with mean 0 and standard deviation 10.

4.2. Error Variance Prior

The error variance, σ^2, is estimated with a non-informative prior that is uniformly distributed between 0 and 10.

4.3. Surgery Type Effects

A covariate for surgery type will be included in the OME model. One surgery type will be designated as the reference surgery, and effects will be estimated for each other surgery type relative to the reference surgery type. The referent surgery type will be the category relating to “abdominal complex” surgeries. Independent normal priors with mean 0 and standard deviation 2 are used for each surgery type effect.

4.4. Time (Era) Effects

The date of randomization for each participant will be adjusted for in the OME model. Sequential 13-week time eras will be defined from the most recent date of randomization for those with complete HFD outcomes backwards in time to the start of randomization. The time eras are set based on the endpoint with the longest follow-up (currently HFD). The intention is that the time era buckets are defined with the same time cutoffs for all analysis models. The most recent time period is the 13-week period preceding the most recent randomization of patients with complete HFD outcomes and

is considered the reference group in the model. Details of the priors for the time era effects are specified in the Core ADR.

4.5. Age Effects

Age will be categorized into three groups: 1) Age 40 or lower, 2) Age 41 to 60, and 3) Age 61 or higher. The middle age group, 41 to 60, will be the reference group. Effects will be estimated for the remaining groups with independent normal priors with mean 0 and standard deviation 2.

4.6. Sex Effects

Sex will be adjusted for in the HFD model. Males will be the reference group, and effects will be estimated for all remaining groups with independent normal priors with mean 0 and standard deviation 2.

4.7. Hospital Effects

The model includes an adjustment for HFD outcomes by hospital. At the first adaptive analysis, the largest hospital is selected as the reference group, and all other hospital effects are estimated relative to the reference. All hospital effects are given independent normal priors with mean 0 and standard deviation 2.

4.8. Preoperative Health Score

The model includes an adjustment for the baseline American Society of Anaesthesiologists' (ASA) score of each participant. The ASA score is a subjective assessment of a participant's overall health that spans from level I (completely healthy) to level V (not expected to survive 24 hours). The reference group for the covariate effects will be Level I, and effects will be estimated for every category relative to the reference group. Each effect will be estimated with independent normal priors with mean 0 and standard deviation 2. If there are any ASA score categories with zero patients, the effects for those categories will be fixed to zero.

4.9. Opioid Tolerance

The model includes an adjustment for baseline opioid tolerance of each patient. An indicator is defined that is equal to 1 if the patient is opioid tolerant and equal to 0 otherwise. The effect of opioid tolerance on OME will be estimated with a normally distributed prior with mean 0 and standard deviation 2.

4.10. Domain Randomization Effects

A covariate for domain randomization will be included for the Analgesia and PONV domains in the OME model. Independent normal priors with mean 0 and standard deviation 2 will be used for each domain randomization effect. If other domains are added to the OME model in the future, an effect for randomization to the new domain would be added to the model with the same prior distribution.

4.11. Other Domain Intervention Effects

The OME model will adjust for randomization assignment within the PONV domain. The A1 intervention will be the reference intervention, and treatment effect will be estimated for A2 relative to A1. Independent normal priors with mean 0 and standard deviation 2 will be used for each intervention effect.

If other domains are added to the OME model in the future, the default prior for intervention effects would be a normal prior with mean 0 and standard deviation 2. Modeling details for new domains, including deviations from this default prior, will be specified in the Current State of the Statistical Models document.

4.12. Analysis Population

The OME model will be analyzed in the OME modified ITT population. This population consists of all participants who have undergone surgery that are randomized to at least one intervention within the Analgesia or PONV Prophylaxis domains. If new domains are added to the OME model, the OME ITT population may be expanded to include additional domains. Any modification of the OME 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 OME model.

5.2. Allocation

Response adaptive randomization will be used in this domain. Initially, participants will be randomized equally between the five interventions (1:1:1:1:1). RAR will be initiated after certain statistical triggers are met (defined in Section 6). RAR will be implemented as described in the Core ADR based on the HFD analysis model. The randomization for each participant is based on the probability that each intervention is optimal within the domain. We use $O(j)$ to denote the probability that intervention $j \in 1, \ldots, J$ is optimal in this domain. The probability a participant is randomized to intervention j in the domain is denoted $\rho(j)$ and calculated as:

$$\rho(j) = (1 - w)O(j) + (w)\left(\frac{1}{J}\right).$$

Where J is the number of arms that are available in the domain. For this domain, the weight w is set to 0.2 resulting in a minimum RAR proportion of approximately 5% with 5 interventions in the domain.

6. STATISTICAL TRIGGERS

This domain specifies two levels of statistical triggers. The first level involves triggers defined among the single agent interventions B1-B3. The statistical triggers in the first level are evaluated until specific conditions are met. At that time, the second level of statistical triggers will be opened as well as RAR.

The first level of statistical triggers include:

- Superiority of Single Agent Interventions
- Inferiority of Single Agent Interventions
- Equivalence of Single Agent Interventions
- Futility of Combination Agents compared to Single Agent Interventions

Each of these triggers are defined below in Sections 6.1 – 6.4.

The second level of statistical triggers include:

- Intervention superiority
- Intervention inferiority

- Equivalence of combination therapies

These triggers are defined below in Sections 6.5 - 6.7.

Prior to moving into the second level of adaptations, one of the following conditions must be met:

- Superiority of one of the single agents
- Inferiority of one single agent and equivalence of the other two agents
- Equivalence of all three single agents

If at an interim, one of the above conditions is met, then the second level statistical triggers and RAR will be evaluated at the same interim. Figure 1 illustrates the conditions needed to move between the two levels of triggers.

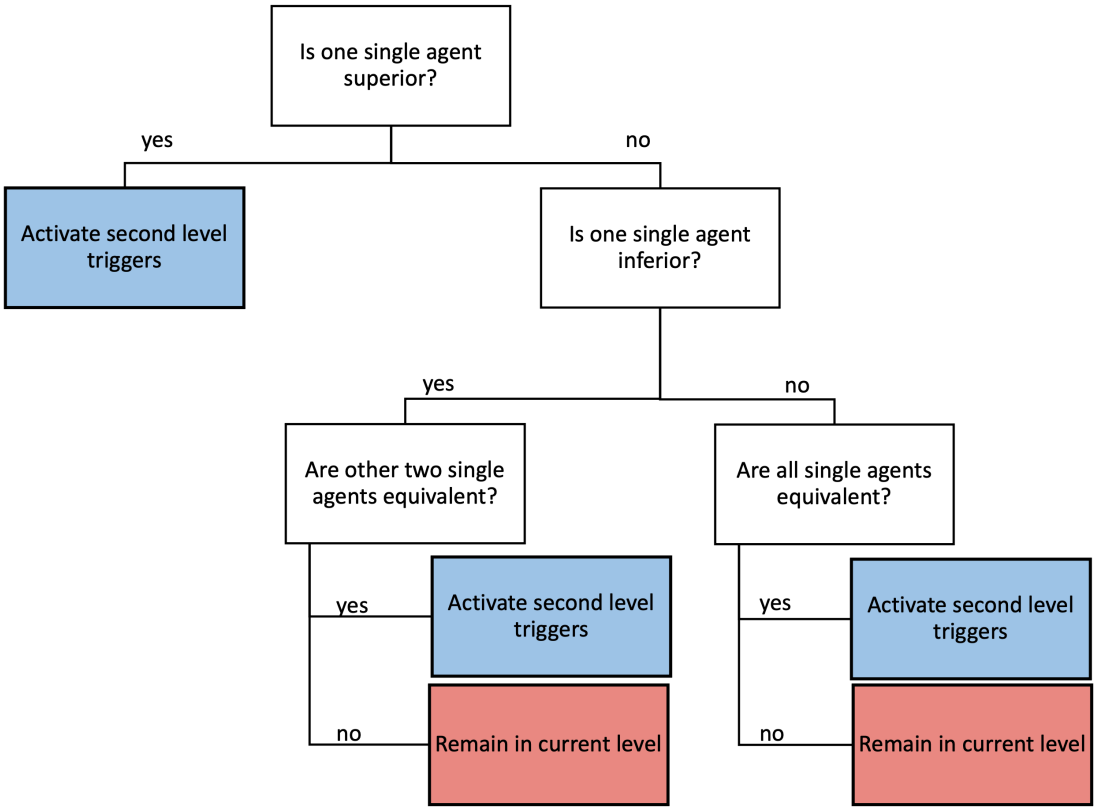


Figure 1: Flowchart of the first level of statistical triggers for the OME domain. Illustrates the ways to move to the second level of statistical triggers.

6.1. Superiority of Single Agent Interventions

This domain includes a statistical trigger of superiority of each single agent intervention (B1, B2, B3) relative to all other single agent interventions. If, at any interim analysis, any single agent intervention has a posterior probability of 99% or greater that it is optimal compared to the other single agent interventions, then that intervention would be declared superior. Upon meeting the statistical trigger, the inferior single agent arms may be dropped, and results would be publicly disclosed. This statistical trigger is applied to the OME endpoint.

6.2. Inferiority of Single Agent Interventions

This domain includes a statistical trigger of inferiority of each single agent intervention (B1, B2, B3) relative to all other single agent interventions.. If, at any interim analysis, one intervention has a posterior probability that it is optimal of 0.01 or lower, then that intervention 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 OME endpoints, and inferiority would be declared upon meeting the trigger for either of the two endpoints.

6.3. Equivalence of Single Agent Interventions

This domain includes a statistical trigger for OME equivalence for each comparison of two single agent interventions within the domain. For OME, the equivalence trigger is defined as a greater than 90% probability that the treatment effect comparing the two interventions is between –0.15 and 0.15 on the log scale. On the original OME scale, this represents a high probability that the difference in OME values between the two interventions is less than ~15%. Upon meeting the statistical trigger for equivalence, one of the equivalent interventions may be dropped and/or a public disclosure is made.

6.4. Futility of Combinations

For each of the combination interventions in this domain (B4/B5), a futility trigger is defined for OME relative to the single agent components of the combination. Specifically, B4 is compared to B1 and B2, and B5 is compared to B1 and B3. If there is a high probability that the combination does not significantly improve outcomes relative to the better of the two single agent components, the combination intervention would be declared to be futile. For OME, the futility trigger is defined as a greater than 95% probability that the treatment effect for each combination relative to the better of

the two components is greater than –0.15 on the log scale. This corresponds to a high probability that the combination reduces OME by less than ~15% compared to the better single agent. Upon meeting the statistical trigger for futility, the futile intervention would be dropped, and a public disclosure would be made.

6.5. 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. Upon meeting the statistical trigger, all other active arms are dropped, and results would be publicly disclosed. This statistical trigger is applied to both HFD and OME endpoints, and superiority would be declared upon meeting the trigger for either of the two endpoints.

6.6. Intervention Inferiority

This domain includes a statistical trigger of inferiority for each intervention within the domain. If, at any interim analysis, one intervention has a posterior probability that it is optimal of 0.01/(J-1) or lower where J is the number of interventions in the domain, then that intervention 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 OME endpoints, and inferiority would be declared upon meeting the trigger for either of the two endpoints.

6.7. Equivalence of Combination Interventions

This domain includes a statistical trigger for OME equivalence for the comparison of the two combination interventions (B4 and B5) within the domain. The same equivalence criteria is used for the interventions B4 and B5 as described in 6.3.

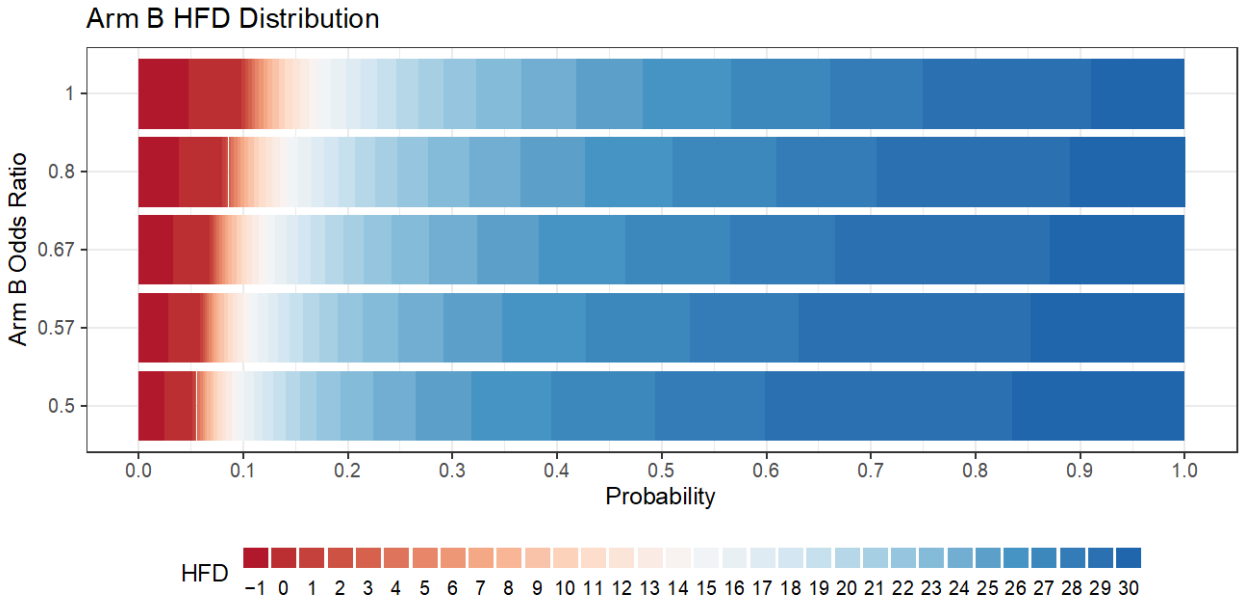
7. DOMAIN OPERATING CHARACTERISTICS

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 OME endpoints. These simulations are restricted to the Analgesia domain of the platform.

7.1. HFD Scenarios

The assumptions for the baseline HFD distribution are based on existing data for elective surgery patients within the UPMC system. The HFD distribution on B1 is based on the HFD outcome rates observed in the available data. A range of treatment effects are explored for each intervention B2-B5 relative to intervention B1. The treatment effects are HFD odds ratios (OR) for each intervention relative to B1. An odds ratio of 1 indicates no difference in HFD outcomes between the two interventions. Odds ratios below 1 indicate the intervention reduces the odds of worse HFD outcomes compared to B1. The figure below visualizes the HFD distribution for each treatment effect scenario.



The table below summarizes the treatment effect scenarios across the 5 interventions in the domain in terms of the HFD odds ratio relative to B1.

Scenario	**B1**	**B2**	**B3**	**B4**	**B5**
Null	1	1	1	1	1
B1 Worst 0.80	1	**0.80**	**0.80**	**0.80**	**0.80**
B1 Worst 0.67	1	**0.67**	**0.67**	**0.67**	**0.67**
B1 Worst 0.57	1	**0.57**	**0.57**	**0.57**	**0.57**

B5 Best 0.80	1	1	1	1	**0.80**
B5 Best 0.67	1	1	1	1	**0.67**
B5 Best 0.57	1	1	1	1	**0.57**
Escalating	1	**0.80**	**0.67**	**0.57**	**0.50**
Combos Additive	**1**	**0.80**	**0.80**	**0.80**	**0.67**
Combos Futile	1	**0.80**	**0.67**	**0.80**	**0.67**

7.2. OME Scenarios

The base case for the distribution of the log(OME+1) outcome is an assumption of normally distributed with mean 4.45 and standard deviation 0.74 based on the distribution estimated from existing data. On the OME scale, this corresponds to a median of 85 and a 95% prior credible interval of (19, 364). Relative to this base scenario, we explore a range of treatment effect patterns across the interventions within this domain. The treatment effects are implemented as mean differences on the scale of the transformed OME outcome which correspond with approximately 10%, 20%, 30%, and 40% reductions in OME relative to the base case above. The table below summarizes the treatment effect scenarios across the 5 interventions in the domain.

Scenario	**B1**	**B2**	**B3**	**B4**	**B5**
Null	0	0	0	0	0
B1 Worst 10	0	**-0.105**	**-0.105**	**-0.105**	**-0.105**
B1 Worst 20	0	**-0.223**	**-0.223**	**-0.223**	**-0.223**
B5 Best 10	0	0	0	0	**-0.105**
B5 Best 20	0	0	0	0	**-0.223**
B3/B5 Same	0	0	**-0.223**	0	**-0.223**
Escalating	0	**-0.105**	**-0.223**	**-0.357**	**-0.511**
Combos Best	**-0.105**	**-0.105**	**-0.105**	**-0.223**	**-0.223**
Combos Futile	0	**-0.223**	**-0.105**	**-0.223**	**-0.105**

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 Analgesia domain. In the simulations, the quarterly adaptive

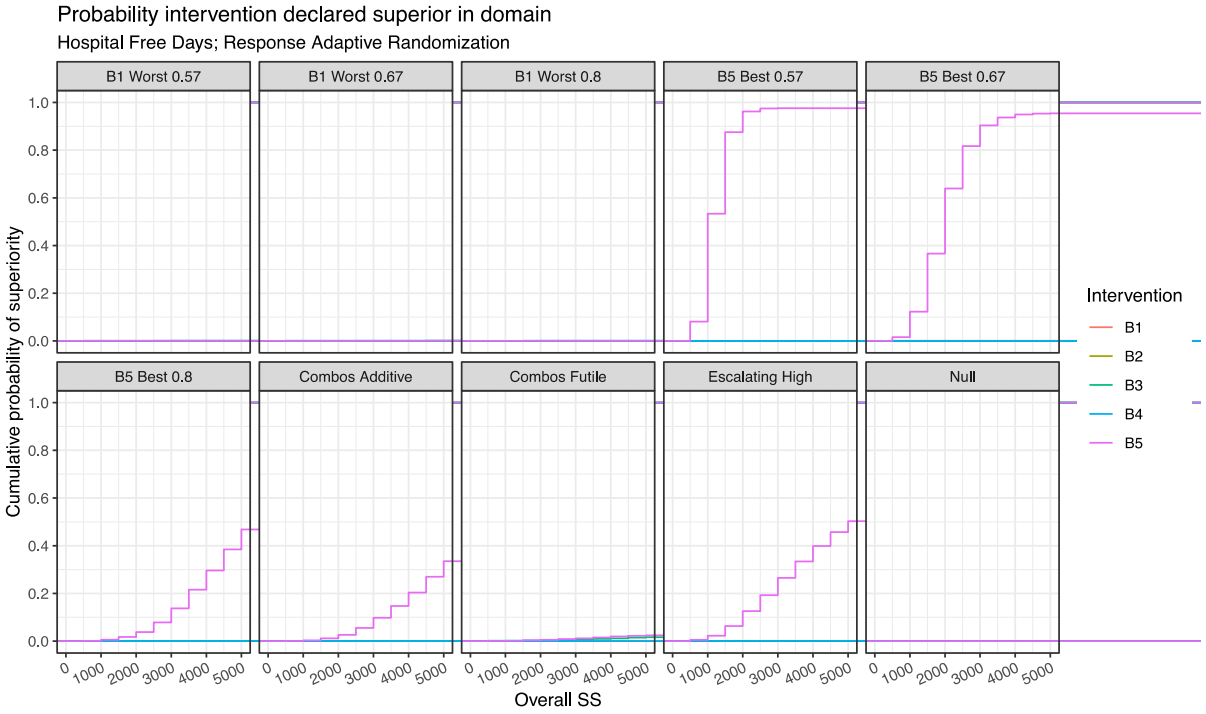
analyses are approximated by analyses conducted every 500 patients with complete outcomes. Simulations are performed separately for each domain endpoint (HFD and OME). These simulations do not incorporate missing data. Covariates are not simulated or incorporated into the statistical model in these simulations. For each simulation scenario, we simulate 5000 trials.

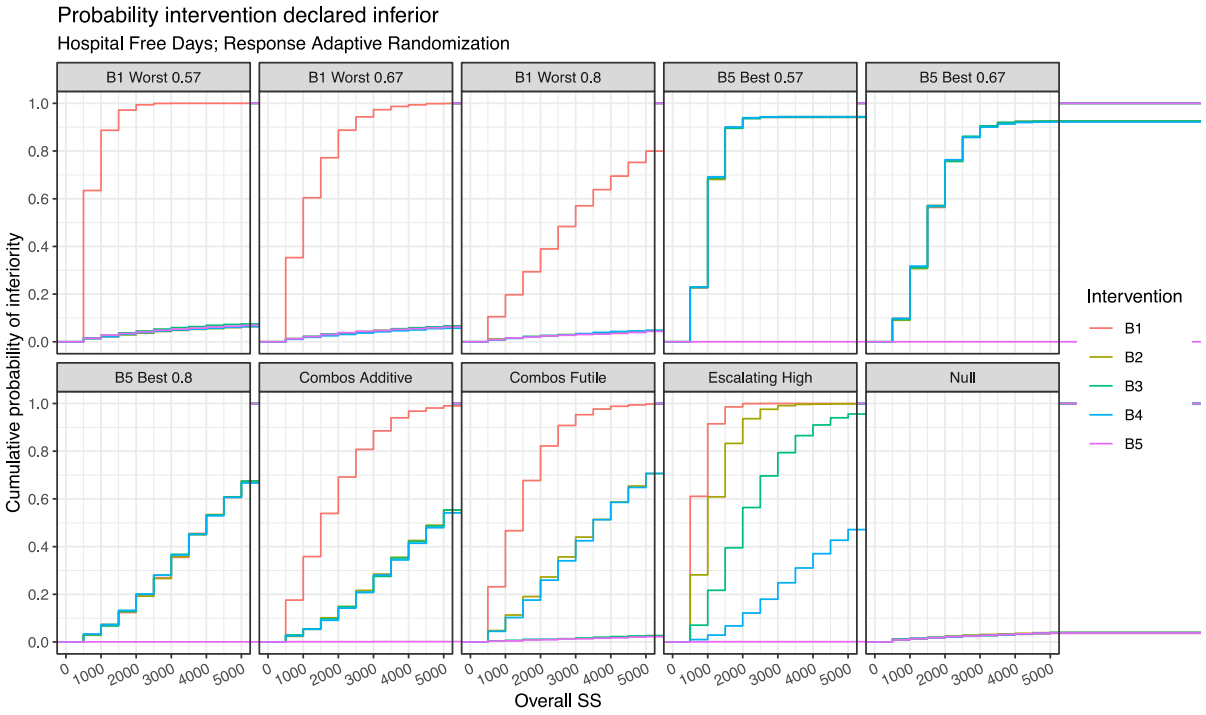
In the simulations of the HFD endpoint, the superiority and inferiority statistical triggers are applied. In the simulations of the OME endpoint, all domain statistical triggers are applied (superiority of single agents/ inferiority of single agents/ equivalence of single agents/superiority/inferiority/futility/equivalence). The statistical triggers are applied in the two levels described in Section 6. In the simulations, we assume that any intervention that is declared inferior or futile is dropped. If an intervention is declared superior within the domain, we assume all remaining arms are dropped. If an intervention is declared as the superior single agent intervention, the remaining single agents are dropped, and any active combination interventions are retained. No action is taken in the simulations if equivalence is hit between two single agent interventions.

Within this domain, RAR is updated based on the comparative effectiveness of each intervention on HFD. In the simulations of HFD, RAR is implemented as described in Section 5.2 and initiated only after one of the conditions outlined in Section 6 is made. In the simulations of OME, the HFD endpoint is not directly simulated. However, we explore two allocation methods that approximate the behavior of RAR under two scenarios for the correlation between HFD and OME treatment effects. First, we simulate the domain with allocation based on RAR using the treatment effects in the OME model. This scenario approximates RAR based on HFD assuming perfect correlation between HFD and OME treatment effectiveness. Second, we simulate the domain with equal allocation between the active (non-dropped) arms. This scenario approximates RAR based on HFD assuming that all domain interventions are equivalent in terms of HFD effectiveness.

Each figure below summarizes the cumulative probability of meeting statistical triggers in the domain for each endpoint. The endpoint and allocation method are specified in the caption of each figure. 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. The color of each line indicates the treatment arm to which the trigger applies. For the plots summarizing the cumulative probability of meeting inferiority, both inferiority of the single agents and inferiority across all active arms are summarized in the same plot. This plot is intended to summarize the timing of when arms drop due to any definition of inferiority.

7.3.1. Simulations for Hospital Free Days





7.3.2.Simulations for Oral Morphine Equivalence (OME) Endpoint