Statistical Analysis Plan for the Analgesia Domain

UPMC REMAP: Perioperative Medicine (Periop)

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1 SAP VERSION

The version is in this document's header and on the cover page.

1.1 Version history

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3 INTRODUCTION

This plan details the statistical analyses of the Analgesia domain as outlined in the Core Adaptive Design Report (ADR) and Analgesia Domain ADR. The ADRs outline analysis conventions for the overall platform and the domain, specifically, related to the primary and key secondary endpoints in the platform. This plan is prespecified for the unblinding of the data for the interventions in the Analgesia domain. The authors of this SAP are blinded to individual data but have been informed by the trial monitoring committee that prespecified statistical triggers have been met for some interventions in this domain. At the first interim analysis conducted, the neuraxial intervention was superior among single agent interventions in terms of oral morphine equivalents but inferior to the combination interventions on hospital-free days. As a result, as part of the prespecified adaptive design, the three single agent interventions were dropped and randomization continues between the two combination interventions. This SAP summarizes the prespecified analyses to be conducted once the remaining interventions have met a conclusion. The primary analysis for this SAP will be conducted once the last patient randomized has completed 30-days of follow-up on the primary endpoint.

4 DESIGN CONSIDERATIONS

Periop explores multiple treatment domains by randomizing patients within multiple domains simultaneously. The adaptive platform trial was designed to produce modular results for individual interventions or full domains upon reaching platform conclusions. Once a predefined statistical trigger is met, the results for the entire domain will be unblinded and made public. This document prespecifies the analysis plan for this unblinding.

Periop is designed with Bayesian analyses for the primary and key secondary endpoints in the trial. For each endpoint, one overarching Bayesian model, prespecified in the Adaptive Design Reports (ADRs), drives all adaptations, statistical triggers, and result summaries across all domains in the platform. The primary and key secondary analysis model will be used to report the results for the interventions in the Analgesia domain.

Periop is a perpetual adaptive platform trial with no planned maximum sample size. Periop defines several statistical triggers within the trial that, at any analysis of the trial, would result in public disclosure and a declaration of a platform conclusion. The following statistical triggers were defined for the Analgesia Domain:

1. Intervention Superiority. If one intervention has a posterior probability of 99% or greater that it is the optimal intervention in the domain, then a declaration of superiority of that intervention would be made. This statistical trigger was applied to the HFD and OME endpoints.
2. Intervention Inferiority. If one intervention has a posterior probability of 1% or lower that it is the optimal intervention in the domain, then a declaration of inferiority of that intervention would be made. This statistical trigger was applied to the HFD and OME endpoints.
3. Single agent inferiority and superiority. As defined above, superiority and inferiority will be evaluated within the single agent interventions alone for the OME endpoint.
4. Single agent equivalence. The single agent interventions will be evaluated for equivalence on OME, defined as a 90% or higher posterior probability of a difference of effects between –0.15 and 0.15.
5. Combination equivalence. The combination interventions will be evaluated for equivalence on OME, defined as a 90% or higher posterior probability of a difference of effects between –0.15 and 0.15.
6. Combination futility. The combination interventions will be evaluated for futility relative to their respective single agent components. Futility is defined as a 95% or higher posterior probability that the difference between the combination effect and the better of the two component single agent effects is less than –0.15.

The simulated operating characteristics for these statistical triggers are described in the Analgesia domain ADR.

5 UNBLINDING

Periop evaluates treatments across multiple treatment domains, and there are currently two domains to which patients are randomized. As the PONV prophylaxis domain has been previously analyzed, all domains/interventions will be unblinded at the time of the Analgesia domain analysis. The predefined primary analysis model will adjust for randomization status in all domains.

6 INTERVENTIONS

There are five interventions included in this domain:

- B1: Neuraxial (intrathecal (IT) morphine)
- B2: Regional Block 1 (paravertebral (PV))

- B3: Regional Block 2 (quadratus lumborum-1 (QL1))
- B4: Neuraxial and Regional Block 1 (IT morphine + PV)
- B5: Neuraxial and Regional Block 2 (IT morphine + QL1)

Interventions B1, B2, and B3 are single agent interventions while B4 and B5 are combinations of the other interventions in the domain. Patients were randomized with fixed, equal randomization (1:1:1:1:1) until the first interim analysis. Response-adaptive randomization between B4 and B5 was utilized after the first interim analysis until the domain was halted.

7 ANALYSIS POPULATIONS

Analyses will be conducted in the following analysis population:

1. Periop modified intention-to-treat (mITT): This population consists of all patients randomized to at least one intervention that have undergone the intended surgery.
2. Single agent concurrent mITT: This population consists of all patients randomized prior to 14 December 2023, the date that the single agent interventions (B1-B3) were halted.
3. Analgesia per protocol. This population consists of all randomized patients that received their assigned intervention in the Analgesia domain.

8 ENDPOINTS

The following end points will be analyzed, displayed graphically, and summarized through descriptive statistics.

1. **Hospital-Free Days** (HFD)
   a. The primary endpoint for the platform is hospital-free days at 30 days after the surgical encounter. HFD is an ordinal composite outcome incorporating death and duration of hospital stay up to 30 days. For patients that survive to 30 days, HFD is calculated by subtracting the total number of days hospitalized from 30, where the number of days hospitalized includes the index hospitalization and any subsequent readmissions up to day 30. Death within 30 days after surgery is recorded as the worst possible outcome in the ordinal scale. The possible values of HFD are, from worst to best: Death (labeled with –1), 0, 1, …, 30 (zero days hospitalized).

2. **Oral morphine equivalents (OME)**

a. OME within 24 hours of surgery is the key secondary endpoint for this domain. 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 (log-transformed) continuous endpoint.

3. **30-day mortality**
   a. A dichotomous endpoint of death within 30 days of surgery. This endpoint corresponds to the –1 component of HFD.
   b. If fewer than 10 deaths have been observed in either of the two treatment groups, this endpoint will be summarized descriptively, and no analyses will be performed.

9 DESCRIPTIVE SUMMARIES

1. Continuous variables will be summarized using the following descriptive statistics: n, mean, standard deviation, median, interquartile range, minimum, and maximum.
2. Ordinal variables will be summarized by the cumulative frequency of each outcome. The 25th, 50th, and 75th percentiles will be summarized. All ordinal endpoints will be plotted using stacked bar plots and cumulative probability plots.
3. Dichotomous variables will be summarized by the number and proportion in each category.
4. Time-to-event variables will be summarized via Kaplan-Meier estimates and the observed quantiles (2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles, as available). Positive clinical event outcomes will be plotted as the cumulative rate of event, and negative events will be plotted as the cumulative rate of event-free.

10 PATIENT CHARACTERISTICS

Baseline characteristics: The following baseline characteristics will be summarized by randomized assignment in the three analysis populations: age, sex, body mass index, race/ethnicity, risk prediction, risk value, surgery type, preoperative ASA health score, hospital location, ERAS PowerPlan name, procedure grouping, MIS/Open/Converted, total procedure time, preexisting conditions (atrial fibrillation, CAD/MI, CHF, CKD/Acute chronic renal failure, COPD, depression, diabetes, GERD, hypertension), opioid tolerance, and tobacco use.

Treatment characteristics: The following variables will be summarized by randomized assignment in the three analysis populations: intra-operative IV lidocaine (yes/no), post-operative IV lidocaine (yes/no), intra-operative IV ketamine (yes/no), and post-operative IV ketamine (yes/no).

11 COMPLIANCE

Compliance will be summarized descriptively by the proportion of patients that received their assigned intervention.

12 ANALYTIC APPROACH

Each inferential analysis will be done using a Bayesian model. A summary of the analyses methods is provided below. The analysis approach is based on the predefined primary analysis model in the platform ADR documents.

12.1 Primary Analysis of Primary Endpoint

The primary analysis model is a Bayesian cumulative logistic model for the ordinal primary endpoint (see Core ADR). The model estimates odds ratio effects for interventions relative to the reference intervention in the domain, where an OR<1 indicates better outcomes. The full details of the model are predefined in the ADRs and the Current State of The Statistical Model document. The model adjusts for variation in outcomes by the following:

- Surgery type
- Age category (≤40, 41-60 (reference), 61+)
- Sex
- Hospital
- Pre-operative ASA score (level I (completely healthy) to level V (not expected to survive 24 hours)
- Time; 13-week buckets of time working backwards from the last enrolled patient.
- Each intervention within each domain

The analyses in this SAP use the following conventions:

- If there are small or empty counts in the HFD outcome, these categories may be collapsed with adjacent levels of the ordinal scale to improve model stability. This may be done within surgery strata to improve model stability.
- All time buckets with <5 patients complete may be combined with the more recent neighboring bucket.
- If there are other covariate groups with <5 patients complete, the covariate may be collapsed to avoid issues with model stability.

12.1.1 Proportional Odds Assumption

The primary analysis model assumes a proportional effect of treatment across the scale of the ordinal outcome. To assess the robustness of the results to this assumption, a dichotomous model is fit to cumulative dichotomizations of ordinal outcome and the treatment effect odds ratio for each dichotomous break is presented. For HFD, odds ratios will be presented for each of the following dichotomous breaks: less than or equal to –1, 7, 14, 21, 22, 23, 24, 25, 26, 27, 28, and 29, respectively. No statistical test of proportional odds is conducted.

12.2 Analytic Approach for Key Secondary Endpoint

The key secondary endpoint is analyzed with a Bayesian linear regression model (see ADRs and Current State of the Statistical Model). The dependent variable is the logarithm of OME plus a constant of one to account for the expected right-skewed distribution and potential zero values of OME. 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. Covariates and prior distributions are specified in the Analgesia ADR and the Current State document.

12.3 Analytic Approach for Other Dichotomous Endpoints

A Bayesian logistic regression model will be used for each additional dichotomous outcome. The model will always specify the "event" as the negative outcome and be parameterized so that an odds-ratio <1 implies benefit to patients. The model is the standard logistic link function model:

$$log\left(\frac{\pi}{1-\pi}\right) = \alpha + [factors]$$

Unless otherwise specified, dichotomous endpoints will include the same covariates as the HFD model. References will be made to the factors in the model and their prior distribution. Many of these factors will be the same as the primary analysis model, with the same priors, as the parameters have similar interpretation. If not otherwise specified, the prior distribution for the main effect is $\alpha \sim N(0, 1.82^2)$ (similar to a uniform prior on the probability scale).

12.4 Markov Chain Monte Carlo (MCMC) Model Stability

The Bayesian models have many parameters and there may be risk of poor model stability, including convergence and mixing behavior of the MCMC sampler. These instabilities may be based on sparse data on the outcome or covariates. The statisticians running the model may make changes that do not

affect the overall interpretation but provide reliable model diagnostics and scientific rigor. Any alterations will be noted.

12.5 Model Outputs

For the ordinal and dichotomous endpoints, the odds-ratios will be summarized. Unless noted otherwise, all models will be parameterized so that an odds-ratio less than 1 indicates clinical benefit. Continuous endpoints will be summarized with the model coefficients which may also be exponentiated. The standard model outputs for each treatment effect will be the posterior median, 95% credible intervals, posterior mean, and posterior standard deviation. All credible intervals will be equal-tailed intervals, so 95% intervals will range from the 2.5^{th} to 97.5^{th} quantile of the posterior distribution.

For each inferential model, a posterior probability that one arm is superior will be provided for each comparison between arms. This posterior probability has been identified as the primary analysis metric between arms.

12.6 Exploratory Analyses

Exploratory analyses not identified in this SAP may be performed to support the clinical understanding of results. Any post-hoc or unplanned analyses that are reported will be clearly identified and will not be evaluated for statistical significance using formal hypothesis tests. Post-hoc exploratory analyses may use the following methods (or similar Bayesian versions of each analysis method):

- Ordinal endpoints will be compared using a cumulative proportional odds model with summaries of the odds-ratio and 95% confidence intervals.
- Time-to-Event analyses will utilize a Cox proportional hazards model (or Bayesian piecewise exponential model), summarizing the hazard ratios and 95% confidence intervals.
- Continuous endpoints will compare means with 95% confidence intervals based on two-sample t-test procedures.
- Dichotomous proportions will be compared using logistic regression summarizing the odds-ratio and 95% confidence intervals.

12.7 Missing Data

Missing outcome data is expected to be minimal, and no imputation of missing outcome data is planned for analyses. If any patients are missing covariate values, these will be imputed based on the modal value at a given site.

13 SPECIFIC PROSPECTIVE ANALYSES

The specific prospective analyses are summarized in the table and described in detail below.

#	Status	Population	Endpoint	Other
1	Primary	Periop mITT	HFD	
2	Key Secondary	Periop mITT	OME	
3	Primary (Component)	Periop mITT	30-day mortality	Same model as HFD.
4	Sensitivity	Periop mITT	Dichotomized HFD	A logistic regression will be run for several dichotomizations of HFD as a robustness check.
5	Sensitivity	Periop mITT	OME	Sensitivity analysis addressing log-transformation (Box-cox transformation and/or sqrt transformations will be explored)
6	Secondary	Analgesia Per Protocol	HFD	
7	Secondary	Analgesia Per Protocol	OME	
8	Secondary	Single agent concurrent mITT	HFD	
9	Secondary	Single agent concurrent mITT	OME	
10	Secondary	Single agent concurrent mITT	30-day mortality	
11	Subgroup	Periop mITT	HFD	Differential effect by surgery Powerplan
12	Subgroup	Periop mITT	OME	Differential effect by surgery Powerplan
13	Subgroup	Periop mITT	HFD	Differential effect by surgery subtype (11 groupings)
14	Subgroup	Periop mITT	OME	Differential effect by surgery subtype (11 groupings)
15	Subgroup	Analgesia Per Protocol	HFD	Differential effect by surgery Powerplan
16	Subgroup	Analgesia Per Protocol	OME	Differential effect by surgery Powerplan
17	Subgroup	Analgesia Per Protocol	HFD	Differential effect by surgery subtype

18	Subgroup	Analgesia Per Protocol	OME	Differential effect by surgery subtype
19	Subgroup	Periop mITT	HFD	Differential effect by prior opioid exposure (yes/no)
20	Subgroup	Periop mITT	OME	Differential effect by prior opioid exposure (yes/no)
21	Subgroup	Analgesia Per Protocol	HFD	Differential effect by prior opioid exposure (yes/no)
22	Subgroup	Analgesia Per Protocol	OME	Differential effect by prior opioid exposure (yes/no)
23	Subgroup	Periop mITT	HFD	Differential effect by surgery type (MIS vs open)
24	Subgroup	Periop mITT	OME	Differential effect by surgery type (MIS vs open)
25	Subgroup	Analgesia Per Protocol	HFD	Differential effect by surgery type (MIS vs open)
26	Subgroup	Analgesia Per Protocol	OME	Differential effect by surgery type (MIS vs open)
27	Sensitivity	Periop mITT	HFD	No site adjustment
28	Sensitivity	Periop mITT	OME	No site adjustment
29	Sensitivity	Periop mITT	HFD	No covariate adjustment, keep intercepts by surgery type
30	Sensitivity	Periop mITT	OME	No covariate adjustment (except for surgery type)
31	Sensitivity	Periop mITT	HFD	Prior on treatment effect is N(0, 10)
32	Sensitivity	Periop mITT	OME	Prior on treatment effect is N(0, 10)

13.1 Reporting of Analysis Results

For each analysis model, the following summaries will be reported when applicable:

Parameter	Posterior Summary			
	Median	95% Credible Interval	Mean	Standard Deviation
Age ≤40				
Age 41-60				
Age 61+				
Female (vs male)				
Time Bucket t (for t in 1, …, T)				
Hospital h (for h in 1, …, H)				
Surgery type s (for s in 1, …, S)				

Pre-Surgery ASA Score (I-V)				
Opioid tolerance (covariate effect in OME model)				
Regional Block 1 (vs neuraxial)				
Regional Block 2 (vs neuraxial)				
Neuraxial + Regional Block 1 (vs neuraxial)				
Neuraxial + Regional Block 1 (vs Regional Block 1)				
Neuraxial + Regional Block 2 (vs neuraxial)				
Neuraxial + Regional Block 2 (vs Regional Block 2)				
Neuraxial + Regional Block 2 (vs Neuraxial and Regional Block 1)				
Main effect of subgroup (if applicable)				
Treatment effect by subgroup (if applicable)				

For each analysis model, the following comparisons will be made, when applicable:

- All interventions will be compared for superiority and inferiority. A 99% or higher posterior probability that an intervention is optimal will be used to define superiority. A 1% of lower posterior probability that an intervention is optimal will be used to define inferiority. Superiority and inferiority will be evaluated for HFD and OME. In subgroup analyses, these probabilities will be provided by subgroup.
- All single agent interventions will be compared for superiority and inferiority on OME. These conclusions will be defined as described above but the comparison will be restricted to the three single agents.
- Pairwise comparisons of the single agents will be conducted for equivalence on OME. Equivalence is defined as a 95% or higher posterior probability that the difference in coefficients is between –0.15 and 0.15.
- B4 and B5 will be compared for equivalence on OME. Equivalence is defined as a 90% or higher posterior probability that the difference in coefficients is between –0.15 and 0.15.
- B4 and B5 will be compared to their single agent components for futility on OME. Futility is defined as a 95% or higher posterior probability that the difference between the combination effect and the better of the two single agent effects is less than –0.15.
- For the sensitivity analysis assessing the proportional odds assumption, the ORs will be summarized for each dichotomization of HFD.