Strategies to Promote ResiliencY - Metformin Trial Statistical Analysis Plan:

An Adaptive Randomized Clinical Trial of Metformin in High-Risk Surgical Patients

UPMC REMAP: Randomized, Embedded, Multifactorial Adaptive Platform Trial for Optimizing Surgical Outcomes

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SIGNATURE PAGE

Approvers:

DocuSigned by:
D633E5594597422...

Matthew D. Neal, MD FACS

9/7/2023

Date

DocuSigned by:
Melanie Quintana
3AEF768DEF9341E...

Melanie Quintana, PhD

9/6/2023

Date

1. UPMC REMAP – SPRY - METFORMIN DOMAIN SAP VERSION

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1.1. Version history

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2. SAP AUTHORS

Jason Kennedy, Cheryl Moore, Matthew Neal, Melanie Quintana, Katherine Reitz, Kert Viele, Hasan Nassereldine

3. INTRODUCTION

The population is aging. Over 50 million Americans are greater than 65 years of age.[1] Associated with, but independent of aging, the cumulative effects of medical, social, and environmental stressors lead to frailty.[2–4] The physiologic stress associated with the surgical treatment of disease is an age and frailty accelerating physiologic stressor, progressing frailty and further depleting resilience.[5,6] As such, aging and frail patients, whom undergo over one third of all surgical interventions, have an increased risk of postoperative morbidity and mortality for all levels of physiologic surgical stress.[4,7–11]

Strategies to Promote ResiliencY (SPRY) aimed to use the age and frailty inducing surgical intervention as an efficient experimental model to stabilize or even reduce frailty and the associated adverse postoperative outcomes. Using a randomized, embedded, multifactorial, adaptative platform (REMAP)[12] trial strategy, we hypothesized that the pleiotropic and anti-inflammatory properties of metformin administered to non-diabetic patients in the perioperative period would reduce the age-accelerating physiologic stress as demonstrated through an increase in postoperative 90-day hospital free days (HFD) following an elective, major surgical intervention.[13]

4. DESIGN CONSIDERATIONS

SPRY investigates the effects of perioperative metformin on the primary outcome of 90-day HFD by pragmatically randomizing patients with different preoperative exposure durations to placebo or one of three doses of metformin. We planned to evaluate three preoperative exposure durations (short, 7-28 days; intermediate, 29-90 days; and long, 90 days) as well as three doses of metformin extended release (ER; 500mg, 1000mg, and 1500mg) among patients undergoing 14 surgical types (i.e., surgical strata). The primary Bayesian model, prespecified prior to patient enrollment, is a Bayesian ordinal logistic regression to estimate the effect of dose and duration of metformin on the distribution of HFD under placebo adjusting for expected differences given the surgical type/strata. Due to early discontinuation of the trial, 14 planned surgical types were consolidated into 6 surgical categories and three perioperative exposure durations were consolidated into one category for the primary Bayesian model.

In response to the COVID-19 pandemic, SPRY temporarily closed enrollment on 3/20/2020. On 8/17/2020, SPRY continued to enroll through in-person clinic-based screening and enrollment but

expanded to also complete virtual patient screening and enrollment. As a result, two enrollment strategies were utilized – in-person and virtual enrollment.

Prespecified adaptive randomization strategies for dose and duration dropping as well as thresholds for treatment efficacy, inferiority, futility, and equivalence were defined for interval analysis with 500 patients enrolled and for every additional 500 patients up to 2,500 followed for 90 days. The complete description of the *a priori* statistical analysis plan was completed prior to patient enrollment and previously published.[13] However, the trial was discontinued prior to the first interval analysis due to low enrollment in the setting of COVID-19 and poor tolerance of perioperative study drug. As such, no interim results triggered response adaptive randomization. As previously planned, trial termination would result in public disclosure and a declaration of results.

5. UNBLINDING

The original intent was for the timing of unblinding to be determined by completion of predetermined endpoints by all subjects enrolled. Unblinding at the time of completion of secondary endpoints was not considered due to the possibility of their occurrence very early in the trial. As SPRY has closed prior to enrolling the goal number of subjects, unblinding will not occur until the statistical analysis plan described in this document is finalized.

6. INTERVENTIONS

There is one active intervention and one control within this analysis plan:

1- Metformin
2- Placebo

Preoperative duration of study drug was pragmatically chosen based upon the time interval between the time of enrollment and scheduled operating room date including:

1- Short – 7-28 days
2- Medium – 29-90 days
3- Long – >90 days

Preoperative duration is not considered in the primary model but was considered in planned sensitivity analyses. Patients were randomly assigned, $\sqrt{}3:1:1:1$ to placebo and the 3 doses of metformin:

1- Placebo
2- Metformin 500mg ER
3- Metformin 1000mg ER
4- Metformin 1500mg ER

The dosing of and route of administration of metformin guidance included to take an oral dose once daily and complete all dispensed medication from the provided pill bottle.

7. DISEASE STATES

The disease state under investigation includes the older (age ≥60) and/or medically frail (age<60 with >2 Charlson Comorbidity Index) non-diabetic patients undergoing a major surgical intervention. Major surgical interventions analyzed include 6 surgical strata:

1- Colon and Rectal Surgery, enrolling from the following clinics
    a. Colon and Rectal Surgery at UPMC Presbyterian University Hospital
    b. Center for Perioperative Care at UPMC Presbyterian Hospital
    c. Center for Perioperative Care at UPMC Shadyside Hospital
    d. Pitt+Me
2- Genera and Oncological Surgery, enrolling from the following clinics
    a. General Surgery at UPMC Presbyterian University Hospital
    b. General Surgery at UPMC Saint Margaret's Hospital
    c. Surgical Oncology at UPMC Presbyterian University Hospital, at Presbyterian
    d. Surgical Oncology at UPMC Presbyterian University Hospital, at Shadyside
    e. General Surgery at UPMC Passavant Hospital
    f. Center for Perioperative Care at UPMC Presbyterian Hospital
    g. Center for Perioperative Care at UPMC Shadyside Hospital
    h. Pitt+Me
3- Orthopedic/Spine Surgery, enrolling from the following clinics
    a. Ortho/Spine Surgery at UPMC Presbyterian University Hospital
    b. Center for Perioperative Care at UPMC Presbyterian Hospital
    c. Center for Perioperative Care at UPMC Shadyside Hospital
    d. Pitt+Me

4- Neurosurgery, enrolling from the following clinics
    a. Center for Perioperative Care at UPMC Presbyterian Hospital
    b. Center for Perioperative Care at UPMC Shadyside Hospital
    c. Pitt+Me
5- Vascular Surgery, enrolling from the following clinics
    a. UPMC East Hospital
    b. UPMC Mercy Hospital
    c. UPMC Saint Margaret's Hospital
    d. Center for Perioperative Care at UPMC Presbyterian Hospital
    e. Center for Perioperative Care at UPMC Shadyside Hospital
    f. Pitt+Me
6- Other, enrolling from the following clinics
    a. Center for Perioperative Care at UPMC Presbyterian Hospital
    b. Center for Perioperative Care at UPMC Shadyside Hospital
    c. Pitt+Me (on-line recruitment)

8. ANALYSIS POPULATIONS

All participants who were randomized and underwent a surgical intervention within 365 days of randomization will be considered in our analysis population.

- SPRY intention to treat (ITT). This population consists of all patients enrolled and randomized to any treatment dose and duration. This population will only include those who underwent a surgical intervention at any time in the 365 days following randomization. All comparisons will be made based up the randomization table allocated treatment.
- SPRY per protocol analysis (PPA): This population consists of all patients enrolled and randomized who also completed randomization table allocated treatment and underwent a surgical intervention within 365 days of enrollment. Adherence to the protocol is determined by those who confirmed compliance with study drug at their 90-day postoperative evaluation with the study team. Compliance is defined by the verbal confirmation of study drug completion at the 90-day follow up timepoint.

9. ENDPOINTS

The following endpoints will be analyzed, displayed graphically, and summarized through descriptive statistics. Endpoints will be reported among the analysis populations as well as among the pre-specified subgroups. Categorical endpoints may be collapsed where appropriate in case of data sparseness.

9.1. Primary Endpoint

The primary endpoint for this domain is the REMAP primary outcome of hospital free days at 90 days after the index date (HFD-90). The index date for HFD-90 outcome is defined as the data of the elective surgical encounter.

Hospital free days Score	Score
-1	Patient died during surgery or within the 90 days following their surgical intervention
0	No days out of the hospital in the 90 days following the surgical intervention
1-90	One to 90 days out of the hospital and alive in the 90 days following the surgical intervention

9.2. Secondary Endpoints

Secondary domain-specific outcome measures include information about EHR based alerts reported during the index elective surgical admission, perioperative outcomes, and surgical outcomes. Specifically, they include:

- Perioperative outcomes (enrollment to postoperative 90 days)
    - Gastrointestinal intolerance (dichotomous; present/absent)
    - SAE as defined in Core Protocol (mild, moderate, severe, life threatening/disabling; adjudicated as related, possibly related, unrelated)

- Surgical outcomes
    - Index admission
        - Postoperative intensive care unit (ICU) admission (dichotomous; any admission/none)
        - ICU length of stay (LOS; continuous, days)
        - Hospital LOS (continuous, days)
        - Discharge disposition (categorical; Home, SNF/LTAC, Death/Hospice)
        - In-hospital mortality (dichotomous; yes/no)
    - 30-day outcomes
        - Organ failure free days (i.e., vasopressor exposure, hemodialysis, or mechanical ventilation; continuous, days)
        - Surgical site infection, as defined by NSQIP and the CDC (categorical)
        - Surgical site occurrence, as defined by Ventral Hernia Working Group (categorical)
    - 90-day outcomes
        - Reoperation/reintervention, both incidence and total number (dichotomous, time to event; any/none and continuous, number)
        - Readmission (dichotomous, time to event; any/none, days)
        - Venous thromboembolic events including deep vein thrombosis and pulmonary embolus after surgery (dichotomous, time to event; any/none, days)
        - Mortality (dichotomous, time to event; yes/no, days)

10. GRAPHICAL DATA SUMMARIES

1. Overall cohort accrual, including number of subjects screened, number excluded for each inclusion/exclusion criteria, and number of subjects per preoperative enrollment category will be presented graphically as a flow/consort diagram.
2. All ordinal endpoints will be plotted using stacked cumulative bar plots and cumulative probability plots.
3. All time-to-event endpoints will be plotted using Kaplan-Meier plots. 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.
4. All continuous endpoints will be plotted using histograms and boxplots.

5. All Bayesian logistic and frequentist logistic regression models will be plotted using forest plots.

11. DESCRIPTIVE STATISTICS

All demographics, baseline characteristics, and perioperative information will be summarized for all randomized participants, the ITT, and PPA analysis populations. Summaries will be presented by treatment group (metformin vs placebo), by treatment and dosage group, and by surgical strata. Data abstracted prospectively throughout the trial, data within trail reporting documentation, as well as data abstracted from the electronic health record will be recorded and included in the summaries. Baseline demographics and characteristics will include age at randomization, sex at birth, race, ethnicity, body mass index, frailty status as measured by the Risk Analysis Index, smoking status, Charlson Comorbidity Index, occurrence of comorbid conditions, preoperative medications, ASA class, surgical strata, and year of randomization. All analyses will be completed both in the ITT and PPA populations.

Primary and supplemental tables will include the following populations:

1- By primary treatment group (Metformin vs placebo)
2- By primary treatment group, separated by dose
3- By primary treatment group, separated by preoperative duration and dose
4- By surgical strata

All endpoints will be modeled following a standard convention based upon the frequency of the events. For interventions with <10 subjects, we will summarize outcomes with No. (%) without modeling due to the small sample size. All analysis will be completed both in the ITT and PPA populations.

1- Ordinal endpoints will be summarized by the number and cumulative frequency of each outcome. The 25^{th}, 50^{th}, and 75^{th} percentiles will be summarized.
2- Dichotomous endpoints will be summarized by the proportion in each category.
3- Composite endpoints will be summarized overall and for each component individually.
4- Time-to-event outcomes will be summarized by the 2.5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, and 97.5^{th} percentiles from the Kaplan-Meier estimates, as available.
5- Continuous endpoints will be summarized by the mean, standard deviation or median, interquartile range (IQR) pending the distribution of the data.

12. TREATMENT DELIVERY

Following randomization, study drug was either provided to the subjects in clinic or study drug was mailed directly to their home. Study drug compliance was monitored at the postoperative 90-day interaction with the study team. At this time, participants who discontinued their medications were determined not adherent and those who continued were adherent. In addition, if patients reported early termination or non-adherence to study drug, this was recorded by study coordinators and reported.

13. ANALYTIC APPROACH

Primary inferential analyses will be done using a Bayesian approach. Sensitivity analyses will be conducted using both Bayesian and Frequentist approaches, as described. Secondary endpoints will be analyzed using frequentist approaches. A summary of the analyses methods is provided below. For all frequentist models, statistical significance will be defined as a one-sided p-value of <0.025, and for all Bayesian models a one-sided posterior probability > 0.975. If stable inference cannot be made due to sparseness of data within strata/categories, data may be further collapsed as needed.

13.1. Primary Analysis of Primary Endpoint

Primary Analysis

The **primary analysis model** is a Bayesian cumulative logistic model for the ordinal primary endpoint. The primary analysis is to be completed in both the ITT and PPA populations described above.

In the primary analysis, observations will be pooled across pre-operative duration of study drug and will borrow across study drug dose. The primary endpoint for this model is HFD-90 and will be compared across the placebo and three levels of study drug dose. The general Bayesian cumulative logistic model is defined below:

Throughout we assume for patient *i,* Y_i is the observed 90-day HFD, $g(i)$, is the surgical strata from 1:G, *d(i)* is the pre-op duration from 1:3 with 1 = short, 2 = intermediate, and 3=long, and *t(i)* is the intervention from 1:4 with 1 = placebo, 2 = 500mg, 3 = 1000mg, and 4 = 1500mg.

The general Bayesian ordinal logistic regression model is used to estimate the effect of dose and duration of metformin on the distribution of HFD-90 under placebo adjusting for expected differences given the surgical strata. The ordinal scale parameterization is a generalized version of the dichotomous parameterization where we model all cumulative probabilities of 90-day HFD being less than or equal to a cut point *c*, where c=–1,…, 89. Given each cut point *c,* we denote the 91 dichotomized versions of 90-day HFD for patient *i* as $Y_{c,i}$ where $Y_{c,i} = 1$ if 90-day HFD is in *[-1, c]* and $Y_{c,i} = 0$ if 90-day HFD is in [c+1,90] for *c=-1,..., 89.* $Y_{c,i}$ is then modeled throughout as:

$$Y_{c,i} \sim Bernoulli(\phi_{c,i});$$

$$logit(\phi_{c,i}) = \gamma_c + \mu_i;$$

where μ_i is a patient-specific mean function and γ_c is common across all patients. To assure model stability, if there is an outcome in the ordinal scale that did not occur in the data, then that outcome will be combined with a neighboring outcome (the worse outcome). For example, if the outcome 11 never occurred, then a combined outcome of 10 & 11 will be modeled for the analysis.

The subject-specific mean function is as follows:

$$\mu_i = \alpha_{g(i)} + \theta_{t(i),d(i)}.$$

Within this model we assume that the underlying distribution of HFD-90 is different within each stratum, *g*, and these differences across strata can be explained by a proportional log-odds ratio shift in the HFD-90 distribution, α_g. Stratum are defined in Section 7. Furthermore, we assume that the effects of each intervention within each pre-op duration are constant across strata and can be explained by a proportional log-odds ratio shift in the HFD-90 distribution $\theta_{t,d}$. Where a log-odds ratio $\theta_{t,d} < 0$ results in an increase in expected HFD-90. For identifiability we assume the effect of placebo across all durations is zero, $\theta_{1,d} = 0 \; for \; all \; d = 1{:}3$. As such, the values of the inverse logit of γ_c define the cumulative probabilities for each HFD-90 value under placebo, common across pre-op durations, and averaged across all strata. For all doses of metformin, we assume that the log-odds ratio of the effect of the dose is dependent on the pre-op duration and takes on the following form:

$$\theta_{t(i),d(i)} = \beta_t + \kappa_d \quad for \; t = 2,3,4 \; and \; d = 1,2,3.$$

Here, β_t is the log-odds ratio due to the dose and κ_d is the log-odds ratio due to the duration. Under the primary analysis where we pool across all pre-op durations we assume $\kappa_d = 0$ for all pre-op durations, $d = 1{:}3$.

The prior distribution of γ_c is specified on the probability scale:

$$\pi \sim Dirichlet(\alpha_{-1}, \cdots \alpha_{90});$$

$$\gamma_c = logit\left(\sum_{i=-1}^{c} \pi_i\right);$$

With hyper-parameters, α_h, specified based on the observed rates of HFD-90 across all strata in pre-trial data (discussed in Section 4) and providing 1 patient worth of information so that $\sum_{h=}^{90} \alpha_h = 1$.

For the strata-specific log-odds ratios we place a normal prior distribution with mean 0 and standard deviation 2:

$$\alpha_g \sim N(0, 2^2).$$

Under the primary analysis, we assume a hierarchical distribution for the dose-effects centered around a common mean so there is borrowing of information across doses:

$$\beta_t \sim N(\mu_\beta, .5^2) \text{ for } t = 2,3,4;$$

$$\mu_\beta \sim N(0,1).$$

Bayesian Sensitivity Analyses

Sensitivity analyses will be conducted in both ITT and PPA populations to assess alternative definitions to degree of study drug exposure. Specifically, the Bayesian cumulative logistic regression with HFD-90 outcome and analysis populations will be conducted for pooling across study drug dose and borrowing across pre-operative duration of study drug. The Bayesian ordinal logistic model will be the same as described above except with the following modifications to $\theta_{t,d}$

$$\theta_{t(j),d(j)} = \beta_t + \kappa_d \quad for\ t = 2,3,4\ and\ d = 1,2,3.$$

Here, β_t is the log-odds ratio due to the dose and κ_d is the log-odds ratio due to the duration. Under the sensitivity analysis where we pool across all active doses we assume $\beta_t = 0$ for all active doses, $t = 2{:}\,4$.

Under the sensitivity analysis, we assume a hierarchical distribution for the pre-op duration effects centered around a common mean so there is borrowing of information across pre-op durations:

$$\kappa_d \sim N(\mu_\kappa, .5^2) \text{ for } d = 1,2,3;$$

$$\mu_\kappa \sim N(0,1).$$

Frequentist Sensitivity Analyses

In addition, sensitivity analyses will be conducted in which frequentist regression models are used in place of the Bayesian cumulative logistic regression and without borrowing across groups. For these analyses, we will assess HFD-90 by 4 definitions of treatment arms based on the intervention, on both the ITT and PPA populations:

1. Treated (any duration and/or dose combined to a single group) vs. placebo
2. Metformin 1500mg ER vs. Metformin 1000mg ER vs. Metformin 500mg ER vs. Placebo (each pooled across duration)
3. Long Metformin (>90 days) vs. Medium Metformin (29-90 days) vs. Short Metformin (7-28 days) vs. Placebo (each pooled across the 3 doses of study drug)
4. Placebo vs. 500mg and 7-28 day duration vs. all other treatment combinations

For each of these definitions, we will apply two approaches:

1. A frequentist proportional odds model for the cumulative odds of 90-day HFD being less than or equal to a cut point *c*, where c=–1,…, 89, as described in the primary Bayesian analysis above. The treatment effect will be estimated, adjusting for surgical strata and duration as covariates.
2. A Mann-Whitney U test with ties for differences in HFD-90 by treatment arm. Test statistics and p-values will be presented. We will report death as a dichotomous outcome (vs. no death) and, among survivors, HFD-90 as a continuous outcome, as outlined in Section 11.

In the logistic regression model, the model structure will be as follows:

$$y_i = logit(\beta_0 + \beta_i * tx\ arm_i + \varepsilon_i);$$

Where:

y_i: Outcome (HFD-90 = 90 vs. ≠ 90) for subject i

β_0 = Coefficient for intercept (for odds of outcome for placebo (reference) group)

β_i = Coefficient(s) for treatment(s) vs. placebo

ε_i = Residual Error for Subject I (i.e. Subject-level random/residual error)

13.1.1. Proportional Odds Assumption

The proportional odds assumption of the treatment effect from the cumulative logistic regression model can be viewed as an average of the individual ORs resulting from dichotomizing at each of the possible cut points of HFD-90. The proportional odds assumption is not required to obtain the average OR estimate; however, this estimate may be a poor summary of treatment effect in the presence of large deviations from proportionality. The degree to which the proportionality assumption is valid will be assessed through visual inspection of the cumulative probability curve across all HFD-90 values within each active treatment arm (when pooling pre-op duration) and within each pre-op duration (when pool active doses) will be compared to the cumulative probability curve under the placebo group. Additionally, we will evaluate the individual ORs under each dichotomization of HFD-90 compared to the overall average OR under the cumulative logistic regression model.

13.2. Analytic Approach for Secondary Endpoints

Primary Analysis

The analysis of secondary endpoints will be conducted with Frequentist methods using unadjusted linear regression, logistic regression, and Cox models for continuous, dichotomous, and time-to-even secondary endpoints, respectively on both the ITT and PPA populations. Secondary endpoints are described in section 9.2 above. Treatment arms will be pooled across all durations and doses to form treated vs. placebo groups, with the placebo group used as the reference category in all analyses. There will be no adjustment for covariates, other than treatment arm.

The model structures will mimic the approach used in the frequentist analysis of the primary endpoint above. Specifically:

Linear regression:

$$y_i = \beta_0 + \beta_i * tx\ arm_i + \varepsilon_i;$$

Logistic regression:

$$y_i = logit(\beta_0 + \beta_i * tx\ arm_i + \varepsilon_i);$$

Cox Regression:

$$h(t|x_i) = h_0(t) * \exp(\beta_i * tx\ arm_i);$$

Where:

y_i or $h(t|x_i)$: Secondary outcome of interest for subject i

β_0 or $h_0(t)$ = Coefficient for intercept or baseline hazard estimate

β_i = Coefficient(s) for treatment(s) vs. placebo

ε_i = Residual Error for Subject I (i.e. Subject-level random/residual error)

Statistical significance will be defined as an unadjusted $p<0.025$. For all models, outputs will be reported using standard conventions and will include regression coefficients, standard deviations, confidence intervals, test statistics, and p-values, as relevant to each model. Model outputs will be reported both graphically and in tables, as described in sections 10 and 13.10.

Sensitivity Analysis

Secondary endpoints will be assessed for alternative definitions of treatment arm. Analyses will mirror the primary analysis of secondary endpoints, replacing the treatment arm with the following alternative definitions:

1. Metformin 1500mg ER vs. Metformin 1000mg ER vs. Metformin 500mg ER vs. Placebo (each pooled across duration) (Primary Approach)
2. Long Metformin (>90 days) vs. Medium Metformin (29-90 days) vs. Short Metformin (7-28 days) vs. Placebo (each pooled across the 3 doses of study drug)
3. Placebo vs. 500mg and 7-28 day duration vs. all other treatment combinations

Model structures will mirror the primary analysis of secondary endpoints and statistical significance

will again be defined as an unadjusted $p<0.025$.

13.2.1. Descriptive Statistics for Secondary Dichotomous Endpoints

In addition to models described above, dichotomous, categorical, and time-to-event endpoints will be reported using descriptive statistics, including number and percent, overall and by strata, as described above in Section 11. Results will be stratified by the definition of treatment used in the primary analysis of secondary endpoints (i.e., treated vs. untreated) only.

13.3. Subgroup Analyses

For the primary outcome of HFD-90 only, subgroups will be evaluated using a frequentist cumulative logistic regression model, as in the primary analysis. These analyses will be conducted on both the ITT and PPA populations and will follow the same approach to pooling across duration and borrowing across dose as in the primary analysis. Analyses will be stratified by each of the following subgroups:

1. Age >= overall median vs < overall median (hypothesis, more effective among those > median)
2. Sex at birth (hypothesis: no difference)
3. Frailty, comparing robust/normal vs. frail/very frail (hypothesis, more effective among frail and very frail). Note that subgroup of robust with normal and frail with very frail may be modified as necessary (e.g., to robust vs. normal/frail/very frail) if sample size for either group is <= 25).
4. Surgical strata (hypothesis, no difference)
    - No operation
    - Spine
    - General surgery/surgical oncology
    - Colorectal Surgery
    - Other
    - Any strata with <= 25 subjects will be combined into the "Other" category, except the "No operation" group
5. Surgical stress (hypothesis, more effective among higher stress procedures)
    - Same day surgery procedures
    - Procedures with subsequent hospital admission

13.4. Exploratory Analyses

Exploratory analyses after unblinding will not be considered inferential. Any *post hoc* exploratory analyses will be clearly labeled as exploratory and will use the conventions below.

1. Ordinal endpoints will be compared using a cumulative proportional odds model with summaries of the OR, 95% credible intervals, and Wilcoxon tests for robustness against a lack of proportional odds.
2. Time-to-Event analyses will utilize a Cox proportional hazards model, summarizing the hazard ratios and 95% confidence intervals.
3. Continuous endpoints will compare means with 95% confidence intervals based on two-sample t-test and/or Mann Whitney U test procedures.
4. Dichotomous proportions will be compared using logistic regression summarizing the OR and 95% confidence intervals. Differences between proportions will be summarized using observed differences and normal approximations for the 95% credible intervals.

13.5. Missing Data Approach

Missing data will be minimized by chart abstraction, as feasible, for missing covariates of all models. Missing data will be reported with number and proportion in summary statistics. For statistical model, where data was not captured, it will be assumed Missing at Random (MAR) and will be imputed as the median value among observed subjects, within strata of dose.

13.6. Multiple Comparisons

No adjustment for multiple comparisons will be made, as the primary analysis model is for a single endpoint and secondary endpoints are intended to provide a broad statistical context for results of the primary analysis model.