Randomized, Embedded, Multifactorial Adaptive Platform for Perioperative Medicine at UPMC

Short Title: UPMC REMAP: Perioperative Medicine (Periop)

ClinicalTrials.gov Number: NCT04606264

Version Number: 1.1

9 JUNE 2023

Version: 1.1, Date: 9JUNE2023

Protocol Revision History

Version Number	Status/Summary of Revisions Made	Version Date
1.0		December 15, 2022
1.1	Addendum added for temporary switch from Aprepitant 40mg PO to 32mg IV	June 9, 2023

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ClinicalTrials.gov Identifier	NCT04606264
IRB study number (Core, DSA)	STUDY19110079, STUDY19030022

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List of Abbreviations

CFR	Code of Federal Regulations
ERP	Enhanced Recovery Protocol
HFD	Hospital Free Days
IRB	Institutional Review Board
MIGS	Minimally Invasive Gynecological Surgery
PI	Principle Investigator
PSM	Patient Safety Monitor
RAR	Response Adaptive Randomization
SAC	Statistical Analysis Committee
SAP	Statistical Analysis Plan
SME	Subject Matter Experts

Master Protocol Summary

Title	Randomized, Embedded, Multifactorial Adaptive Platform for Perioperative Medicine at UPMC
Short Title	UPMC REMAP: Perioperative Medicine (Periop)
Brief Summary	This is a randomized, open label, adaptive platform trial to compare the different strategies for enhancing recovery in the perioperative arena in patients with elective surgical encounters at UPMC who meet eligibility criteria.
Objectives	The objective of this study is to determine the effectiveness of each component of treatment individually as well as in combination with other elements, specific to surgery type. All intervention arms or combinations of interventions follow the key tenets of ERP.
Methodology	Adaptive Randomized Platform Trial
Endpoints	Primary Endpoint: total hospital free days (HFD) at day 30 after the surgical encounter, which is defined as the difference between first 30 days post-surgery and the length of stay in the hospital post-surgery. If the patient was readmitted within the first 30 days postoperatively, HFD will be calculated as difference between first 30 days post-surgery and the length of stay in the hospital post-surgery and the length of stay in the hospital during readmission. Key Secondary Endpoint: postoperative opioid use by measurement of oral morphine equivalents (OME) and postoperative nausea and vomiting (PONV) measured by antiemetic medication use Other Secondary Endpoint: postoperative complications Safety Endpoints: Not applicable as the trial is treatment recommendations to the provider
Study Duration	There is no designated duration. The study will continue until conclusions can be made for each intervention arm.
Participant Duration	30 days from the index elective surgery
Duration of assigned treatment strategy	During index hospitalization for elective surgery
Population	Adult patients having elective surgical encounters within UPMC facilities
Study Sites	UPMC Presbyterian Hospital, UPMC Passavant Hospital, UPMC Magee-Womens Hospital
Number of Participants	There is no set number of trial participants. Participants will continue to be enrolled until conclusions can be made for each domain.
Description of Study Agents	Randomized arms- see appendix This platform trial allows for multiple therapies to be investigated in this trial over time. The trial is governed by a Master Protocol that describes the trial design, endpoint collection, primary endpoint, and inclusion/exclusion criteria. Different therapies, referred to as interventions, are detailed in domain-specific appendices. These domain-specific appendices

	work in a modular fashion as domains or interventions are removed and added to the platform trial.
Key Procedures	Electronic medical record data from 30 days after surgery
Statistical Analysis	Inferences in this trial are based on a Bayesian statistical model, which considers the variation in outcomes by site, surgical procedural grouping, time, and arm of the trial. The specific analyses, including interim analysis schedule, are specified in each domain-specific appendix.

1 Introduction, Background Information, and Scientific Rationale

1.1 Background Information, Significance, and Relevant Literature

ERP at UPMC utilizes a combination of standard of care treatments for patients undergoing surgeries across different surgical specialties including colorectal surgery, general surgery, surgical oncology, pancreas surgery, liver surgery, liver and renal donor surgeries, thoracic surgery, urological procedures, ENT surgeries, endocrine surgeries, bariatric surgery, gynecological oncological surgery, minimally invasive gynecological surgery (MIGS), urological-gynecological surgery, orthopedic surgery and neurological surgeries. Standard of care treatments in perioperative care include therapies to reduce pain (i.e., nonopioid analgesia, nerve blocks, adjunctive pain medications), reduce postoperative nausea and vomiting (i.e., antiemetics, anesthesia type), and optimize patient intravascular volume status (i.e., preoperative oral hydration, intraoperative fluid monitoring). However, these therapies are provided in widely variable combinations as surgical specialty or hospital site utilize variations of standard of care ERP clinical practice. Nonetheless, the care pathways applied to perioperative protocols such as ERP have demonstrated reduced length of stay across numerous surgical specialties (1-3 days reduction), increase in same day discharge rates (MIGS and urological-gynecological surgery), no increase in readmission rates, reduced perioperative morbidity, improved patient satisfaction, and faster recovery to presurgical functional status. Still, the exact combination of therapies that provides the benefit to patients is unknown given the wide clinical practice variation.

1.1.1 Adaptive Design

This platform trial will have multiple arms, which may be dropped or added as the platform trial progresses. Sample size will be flexible: the trial will be stopped for superiority, equivalence, or futility based on pre-determined statistical thresholds as defined in the Adaptive Design Report. Each arm will have a 1:1 randomization or response adaptive randomization as defined in the Adaptive Design Report.

1.2 Potential Risks & Benefits

See arm-specific Appendices for details.

2 Study Design

2.1 Overall Study Design

This trial applies novel and innovative trial adaptive design and statistical methods to evaluate a range of treatment options as efficiently as possible. The broad objective of a REMAP trial is, over time, to determine and continuously update the optimal set of treatments for the topic of interest. The set of treatments that may be tested within a REMAP comprise the set of all treatments that are used currently or may be developed in the future and used or considered for use. The design maximises the efficiency with which available sample size is accrued to evaluate treatment options as rapidly as possible. A REMAP has the capacity to identify differential treatment effects in defined sub-groups (termed strata), address multiple questions simultaneously, and can evaluate interactions among selected treatment options. Throughout the platform, patients who are enrolled in the trial are treated as effectively as possible.[1-6]

2.2 Randomization

Randomization assignments are at the participant level and are assigned before surgery. Some domains may use response adaptive randomization (RAR) to adaptively adjust the allocation proportion to

interventions based on the accruing efficacy data. The data on the primary endpoint (HFD) will determine the randomization proportions for each intervention within the domain.
When a domain is added to the platform, there will be an initial period (the burn-in) in which randomization is fixed and equal for each intervention in the domain. At the first adaptive analysis after the domain is added to the platform, RAR will be used to update allocation for each intervention in the domain.

3 Objectives and Purpose

The objective of this study is to determine the effectiveness of each treatment intervention individually as well as in combination with other elements, specific to surgery type. All interventions or combinations of interventions follow the key tenets of ERP.

This objective will be achieved by recommending a patient-specific ERP combination via randomization of those perioperative interventions commonly used within UPMC facilities to the patient's physician. This recommendation will be provided to the clinical team responsible for the care of the patient via the eRecord system. The clinical team will accept, modify, or reject the recommended ERP interventions, based on the patient's underlying health and good clinical practice.

4 Study Design and Endpoints

4.1 Description of Study Design

This trial applies novel and innovative adaptive design and statistical methods to evaluate a range of treatment options as efficiently as possible. This is an open label randomized trial of patients undergoing elective surgery.

4.2 Study Endpoints

4.2.1 Primary Study Endpoint

Hospital Free Days (HFD). The primary endpoint will be the total hospital free days at day 30 after the surgical encounter. HFD is the difference between first 30 days post-surgery and the length of stay in the hospital post-surgery. If the patient was readmitted within the first 30 days postoperatively, HFD will be calculated as difference between first 30 days post-surgery and the length of stay in the hospital post-surgery and the length of stay in the hospital during readmission. If the patient dies at any point in the 30 day follow up period after the surgical encounter, they will be assigned -1 HFD.

4.2.2 Secondary Endpoints

Key Secondary Endpoints:

- postoperative opioid use by measurement of oral morphine equivalents (OME)
    - OME will be measured as a patient's total OME from post-operative day 0 (POD0) through POD1
- postoperative nausea and vomiting (PONV) measured by antiemetic medication use
    - if a patient received one or more antiemetic medication within the first 24 hours after surgery, they will be considered to have had PONV

Other Secondary Endpoints:

- postoperative complications such as myocardial infarction, cerebrovascular accident, respiratory failure, etc

4.2.3 Additional Study Endpoints

- NA

4.2.4 Safety Endpoints

- Not applicable as the trial is treatment recommendations to the provider

5 Study Enrollment

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- ≥ 18 years of age
- Scheduled for abdominal surgery that utilizes enhanced recovery protocols (ERP)
    - ERAS Abdominal Complex Pathway PowerPlan
    - ERAS Colorectal Pathway PowerPlan
    - ERAS Bariatric Surgery Pathway PowerPlan
    - ERAS Gynecology Oncology Pathway PowerPlan
    - ERAS Whipple/Pancreas Pathway PowerPlan
    - ERAS Open Liver Resection Pathway PowerPlan
- Surgery is scheduled for one of the following UPMC sites:
    - UPMC Presbyterian Hospital
    - UPMC Passavant Hospital
    - UPMC Magee-Womens Hospital

5.2 Exclusion Criteria

An individual is excluded from this study if they meet one of the following criteria:

- Patient is pregnant
- Age < 18 years old

5.3 Strategies for Recruitment and Retention

Patients who meet the above eligibility criteria are automatically enrolled in the trial. Because the interventions are comparing standard of care or better than the standard of care, randomization will occur in the context of a waiver of informed consent. Providers are notified of their patients' participation in the trial and have the option to change any of the recommendations given.

5.4 Duration of Study Participation

Duration of study participation is up to 30 days after surgery date.

Total Number of Participants

The total sample size for the Platform trial is not pre-determined. The sample size for each arm will be set in the adaptive design report. There will be interim monitoring to evaluate for futility, efficacy, or safety. If one intervention proves to be efficacious, then this intervention may become the reference intervention for comparison with newly added interventions within the arm.

5.5 Participant Withdrawal or Termination

5.5.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. Discontinuation of a study agent, regardless of the reason, e.g., patient or physician request, or adverse event, does not constitute study withdrawal. Patient data will still be collected and analyzed as intent to treat unless the participant withdraws consent for continued follow-up.

An investigator may terminate participation in the study if any situation occurs such that continued participation in the study would not be in the best interest of the participant. As the randomization provides recommended treatments only, the investigator can deviate from the recommendations without terminating participation. In this situation, the patient data will still be collected and analyzed as intent to treat unless the participant withdraws consent for continued follow-up.

5.6 Premature Termination or Suspension of Study

All deaths and Patient Safety Monitor (PSM) specified severe adverse events within the study period will be reviewed by the PSM. The decision to stop or suspend the study, or an arm of the study, will be made by the PSM after considering the totality of the data and the benefit-risk of continuing the study.

This study, or an arm of the study, may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants in an intervention, such as excess mortality
- Demonstration of efficacy or lack thereof that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor and/or IRB.

6 Study Agent and Procedural Intervention

6.1 Study Agents

Each arm in this platform trial will include different treatment strategies. Information about the treatment strategies for a given arm can be found in the arm-specific appendices.

6.2 Duration of Therapy

Once participants are randomized to a treatment strategy (arm), they will remain on treatment for the duration specified by the relevant appendix.

Providers have the option to deviate from the randomization assignment if they believe it is medically necessary. All treatments are suggestions for providers.

7 Study Procedures and Schedule

7.1 Study Schedule

Activity	Prior to day of surgery	Hospital duration	30 days post-surgery
Need for surgery is determined	x		
Eligibility is determined	x		
REMAP Periop PowerPlan is placed	x		
Patient arrives on day of surgery		x	
PONV prophylaxis medications and preoperative pain blocks are given		x	
Patient is taken to surgery		x	
Dexamethasone is given at induction of surgery		x	
Ondansetron is given upon emergence from surgery		x	
Post surgery PONV medications are monitored		x	
OME is monitored		x	
Hospital Free Days is calculated			x

7.1.1 Prior to Day of Surgery

1. Patient seen by their surgery team and need for patient to undergo surgery determined.
2. Assessment of inclusion/exclusion criteria completed.
3. REMAP Periop PowerPlan ordered, and randomization assignment given.

7.1.2 Hospital Duration

1. Patient arrived to preoperative holding area.
2. PONV prophylaxis medications given based on randomization assignment.
3. Preoperative pain blocks given based on randomization assignment.
4. During surgery, patient is given Dexamethasone and Ondansetron.
5. Patient treated, as seen necessary, for nausea and vomiting and post-operative pain.
6. PONV medication usage tracked for first 24 hours after surgery.
7. Oral Morphine Equivalence is calculated for first 24 hours after surgery.

7.1.3 30 days Post-surgery

1. HFD is calculated 30 days post-surgery.

7.2 Expedited Critical and Major Event Reporting

All efficacy and safety outcome events will be assessed and documented. The REMAP Periop Trial will have a uniform policy for reporting adverse events to ensure that all events are assessed quickly and are submitted to the PSM and/or IRB, following each group's reporting guidelines and timelines. Events meeting the independent PSM-specified criteria will be reported immediately and within the time frames specified by the PSM.

Sites are required to follow their local reporting guidelines.

7.3 Data and Safety Monitoring Plan

The REMAP Periop Trial will have a uniform Data and Safety Monitoring Plan, encompassing all research carried out within.

8 Statistical Considerations

8.1 Statistical and Analytical Plans

There will be a formal Statistical Analysis Plan (SAP). This will include the primary analysis, the primary comparison, futility and success rules, and interim analysis schedule. The SAP will be created prior to the first interim analysis for the study.

8.2 Sample Size

Sample size for the platform trial is not pre-determined. The platform trial will run as long as there is a need and there are investigational arms enrolling. Interim analyses for each arm will take place in the platform trial and detailed in the arm-specific appendix. Conclusions of futility or superiority may be drawn specific to a patient subtype. Effort will be taken to conduct all interim analyses at the same time in the platform trial since there is a single Bayesian model of the efficacy of all arms conducted. If one strategy proves to be efficacious, then this strategy may become the reference arm for comparison(s) with new experimental treatment(s). New arms can be introduced according to scientific and public health needs.

9 Measures to Minimize Bias

9.1 Enrollment

Patients who meet all inclusion criteria and no exclusion criteria will be automatically enrolled in the trial.

9.2 Randomization

Randomization assignments are performed for participants when their orders for care are placed before surgery. Randomization will be equal across all arms a patient is eligible for the first iteration. After the first interim analysis, RAR will be used.

10 Source Documents and Access to Source Data/Documents

10.1 Source Documents

10.1.1 Document Names, Locations, and Access

All documents involved in REMAP Periop are listed below with their locations and list of personnel who can access and edit the documents.

- Randomized, Embedded Multifactorial Adaptive Platform for Perioperative medicine at UPMC (UPMC REMAP Periop): Core Protocol
    - Location:
        - Microsoft Teams>REMAP Periop>General>Protocols>IRB_Submitted
    - Access:

        - Jennifer Holder-Murray, Stephen Esper, Joshua Knight, Alison Althans, Miranda Masters, Nicole Zharichenko
    - Editing Privileges:
        - Jennifer Holder-Murray, Miranda Masters, Nicole Zharichenko
- Domain Specific Appendix: Enhanced Recovery Protocols (ERP)
    - Location:
        - Microsoft Teams>REMAP Periop>General>Protocols>IRB_Submitted
    - Access:
        - Jennifer Holder-Murray, Stephen Esper, Joshua Knight, Alison Althans, Miranda Masters, Nicole Zharichenko
    - Editing Privileges:
        - Jennifer Holder-Murray, Miranda Masters, Nicole Zharichenko
- REMAP Periop: Core Adaptive Design Report
    - Location:
        - Microsoft Teams>REMAP Periop>General>Protocols>Statistical Analysis Plan
    - Access:
        - Jennifer Holder-Murray, Stephen Esper, Joshua Knight, Alison Althans, Miranda Masters, Nicole Zharichenko, Berry Consultants
    - Editing Privileges:
        - Berry Consultants
- REMAP Periop: Adaptive Design Report for the Analgesia Domain
    - Location:
        - Microsoft Teams>REMAP Periop>General>Protocols>Statistical Analysis Plan
    - Access:
        - Jennifer Holder-Murray, Stephen Esper, Joshua Knight, Alison Althans, Miranda Masters, Nicole Zharichenko, Berry Consultants
    - Editing Privileges:
        - Berry Consultants
- REMAP Periop: Adaptive Design Report for the Post-operative Nausea and Vomiting (PONV) Prophylaxis Domain
    - Location:
        - Microsoft Teams>REMAP Periop>General>Protocols>Statistical Analysis Plan
    - Access:
        - Jennifer Holder-Murray, Stephen Esper, Joshua Knight, Alison Althans, Miranda Masters, Nicole Zharichenko, Berry Consultants
    - Editing Privileges:
        - Berry Consultants
- Statistical Analysis Plan (SAP)
    - Location:
        - Microsoft Teams>REMAP Periop>General>Protocols>Statistical Analysis Plan
    - Access:
        - Jennifer Holder-Murray, Stephen Esper, Joshua Knight, Alison Althans, Miranda Masters, Nicole Zharichenko, Berry Consultants
    - Editing Privileges:

        - Berry Consultants
- Data and Safety Monitoring Plan
    - Location:
        - Microsoft Teams>REMAP Periop>General>Protocols
    - Access:
        - Jennifer Holder-Murray, Stephen Esper, Joshua Knight, Alison Althans, Miranda Masters, Nicole Zharichenko
    - Editing Privileges:
        - Jennifer Holder-Murray, Miranda Masters, Nicole Zharichenko

10.2 Source Data

10.2.1 Data Sources, Locations, and Access

All REMAP Periop data is listed below with it's original source, storage location, and access privileges.

- Interim Analysis Data
    - Original source:
        - Qlik>ERAS Dashboard>Periop REMAP
    - Storage location
        - Microsoft Teams>REMAP Periop>Trial Data>Data
    - Access privileges
        - Miranda Masters, Nicole Zharichenko
- Randomization Assignments
    - Original source:
        - Clinical Analytics
    - Storage location
        - Microsoft Teams>REMAP Periop>Trial Data>Randomizations
    - Access privileges
        - Miranda Masters, Nicole Zharichenko

11 Quality Assurance and Quality Control

The REMAP Periop Trial will have uniform policies for quality assurance at the data entry level and site monitoring.

12 Ethics/Protection of Human Subjects

12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6

12.2 Institutional Review Board

The protocol and all participant materials will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study.

12.3 Waiver of Informed Consent

The research components represent minimal risk activities, so this trial will be conducted in the context of a waiver of informed consent. All interventions being compared are standard of care of greater than the standard of care.

12.4 Participant and Data confidentiality

The REMAP Periop Trial will have uniform policies for protecting the privacy of participants and maintaining confidentiality. These policies will adhere to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

13 Data Handling and Record Keeping

13.1 Data Collection and Management Responsibilities

The REMAP Periop Trial will have uniform policies for data management.

13.2 Study Records Retention

The REMAP Periop Trial will have uniform policies for records retention.

13.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the principle investigator (PI)/study staff to use continuous vigilance to identify and report deviations.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

13.4 Publication and Data Sharing Policy

The REMAP Periop Trial will have uniform policies for publications and data sharing.

14 Study Finances

14.1 Funding Source

The Beckwith Institute:

- Clinical Transformation Program Research Grant: REMAP Periop

National Institutes of Health:

- R01 Grant: Individualized Prediction of Treatment Effects Using data from Both Embedded Clinical Trials & EHR

14.2 Costs to the Participant

Participant health insurance may be billed for the costs of medical care during this study since these expenses would have happened even if the participant were not in the study. If the participant's insurance does not cover these costs, or the participant does not have insurance, these

costs will be participant's responsibility.

15 Conflict of Interest Policy

The REMAP Periop Trial will have uniform policies for identifying and disclosing potential conflicts of interest.

16 References

1. Angus DC. Fusing Randomized Trials With Big Data: The Key to Self-learning Health Care Systems? JAMA 2015;314:767-8.
2. Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. JAMA 2015;313:1619-20.
3. Carey LA, Winer EP. I-SPY 2--Toward More Rapid Progress in Breast Cancer Treatment. The New England journal of medicine 2016;375:83-4.
4. Harrington D, Parmigiani G. I-SPY 2--A Glimpse of the Future of Phase 2 Drug Development? The New England journal of medicine 2016;375:7-9.
5. Park JW, Liu MC, Yee D, et al. Adaptive Randomization of Neratinib in Early Breast Cancer. N Engl J Med 2016;375:11-22.
6. Rugo HS, Olopade OI, DeMichele A, et al. Adaptive Randomization of Veliparib-Carboplatin Treatment in Breast Cancer. The New England journal of medicine 2016;375:23-34.

Appendix 1: Master Protocol State of Arms

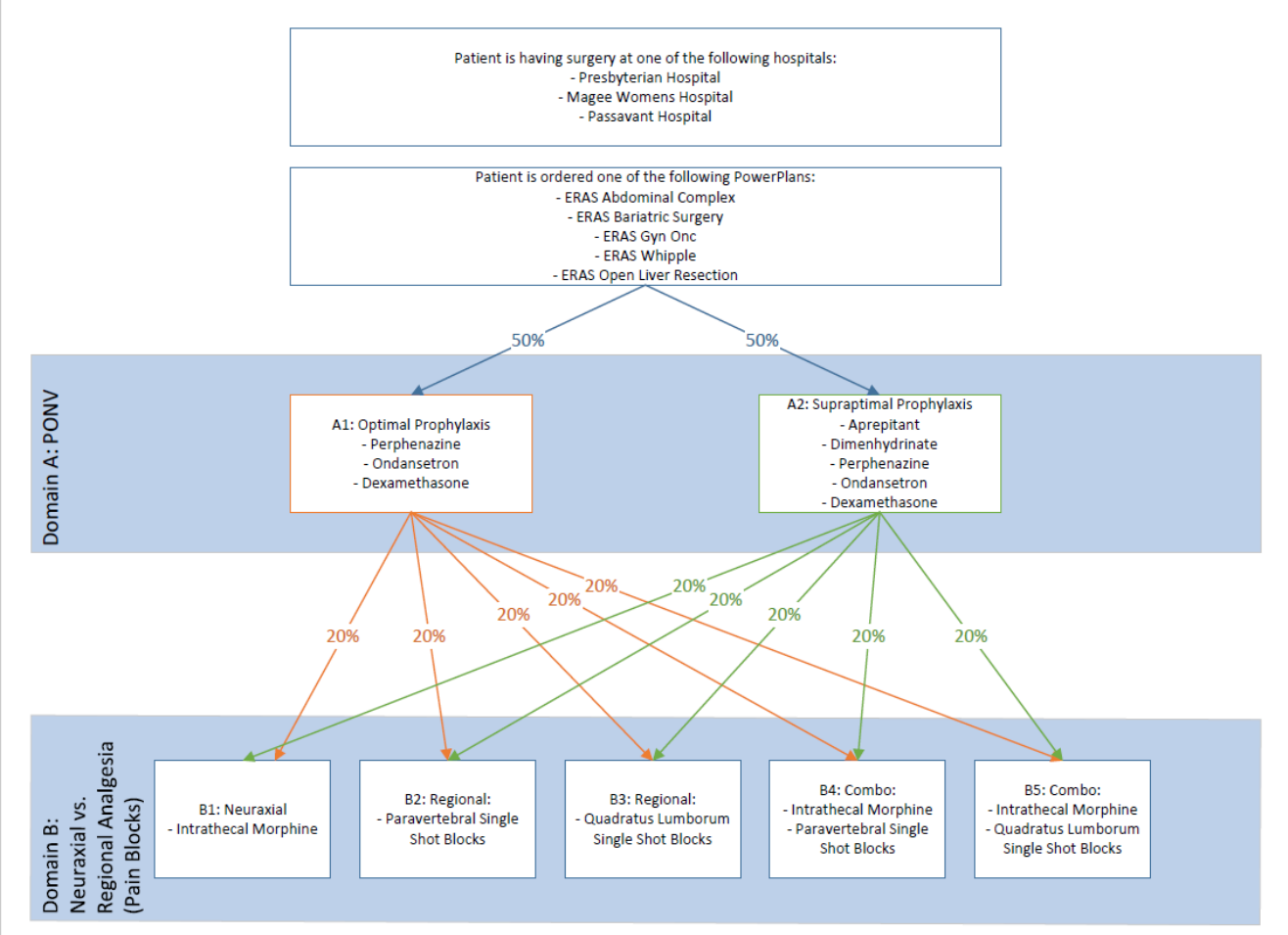
This appendix will be updated as arms are added or dropped. The current version and version history appear below.

Version 15DEC2022: Outlined Domains A and B

Version 9JUNE2023: Adds Addendum 1 explaining the switch from Aprepitant 40mg PO to Aprepitant 32mg IV because of the shortage in Aprepitant 40mg PO.

Randomization

Randomization assignments are at the participant level. The participant will be randomized to one of two interventions from Arm A and one of five interventions from Arm B.



A1.1: Current Statistical Modeling Adaptions

All current statistical modeling can be found in the adaptive design reports.

Appendix 2: Definition and Determination of Outcomes

A2.1 Outcome Definitions

30 Day Hospital Free Days

Defined as the number of days from the day of surgery to the 30 days thereafter, during which the patient is alive and not in the hospital. If the patient dies at any time during the 30-day period, they are assigned the score of -1.

Primary Endpoint

Days not admitted in the hospital within 30 days after surgery. Hospital free days is defined as the number of days patients are not in the hospital during the 30-day period after surgery. This includes readmissions. If the patient dies at any time during the 30-day period, they are assigned the score of -1.

Secondary Endpoints

Postoperative nausea and vomiting (PONV)

PONV is measure by antiemetic medication use within the first 24 hours post-surgery. This will be measured as a dichotomous outcome, denoted as "yes" if any of the following medications are administered to the patient within the 24 hours following surgery: dimenhydrinate, haloperidol, granisetron, ondansetron, prochlorperazine, dolasetron, droperidol, metoclopramide, palonosetron, promethazine, ramosetron, scopolamine, tropisetron, or perphenazine. This data will be abstracted from the medication administration record within the electronic medical record.

Postoperative Opioid Use

Postoperative opioid use is determined by measurement of oral morphine equivalents (OME). Opioid quantities will be converted to oral morphine equivalents (OME), a continuous variable that can be compared amongst patients receiving different types of opioids. Standardized conversion factors for each opioid medication are well described and frequently utilized in literature regarding pain control[1]. OME data will be abstracted from the medication administration record within the electronic medical record. We will measure OME in milligrams per day as a continuous variable for the 24 hours following surgery.

A2.2 References

1. Nielsen S, Degenhardt L, Hoban B, Natasa G. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. *Pharmacoepidemiol Drug Saf*. 2016;25:733-737.

Appendix 3: Postoperative Nausea and Vomiting (PONV) Prophylaxis (Arm A)

PONV is common after surgery occurring in up to 80 percent of cases without prophylaxis. Therefore, PONV prophylaxis guidelines exist to ameliorate this adverse outcome. These guidelines describe multiple ways to treat PONV, and though the number of treatments is proportional to the risk stratification, it does not specifically address which medications, or combinations of medications, are superior. Additionally, even after administration of multiple medications designed to prevent PONV via an ERP, the incidence can be over 40% in certain populations.[1] At UPMC, a 3 medication optimal regimen, which is designed to prevent PONV even in higher risk patients, does not ameliorate PONV to near zero as certain populations still experience PONV after 10 to 40% of surgeries. PONV can then lead to delayed diet intake, increased perception of pain, longer duration of hospital stay, and decreased patient satisfaction. Therefore, improving a PONV prophylaxis regimen beyond our standard ERP 3 medication regimen is imperative. We aim to compare a supraoptimal protocol, designed to target PONV prophylaxis from nearly every biochemical mechanism to our standard, optimal 3-medication regimen to reduce the incidence of PONV.

A. Question:
    a. Is supraoptimal PONV prophylaxis superior to optimal 3 medication PONV prophylaxis?
B. Hypothesis: The administration of supraoptimal PONV prophylaxis is superior to the use of optimal prophylaxis.
C. Comparison/Interventions: Patients will receive either conventional optimal PONV prophylaxis with 3 medications or supraoptimal PONV prophylaxis with 5 medications.
    a. Optimal Prophylaxis (3 medications)
        i. In Pre-op:
            1. Perphenazine 8mg po
        ii. At Induction:
            1. Dexamethasone 4-5 mg IV
        iii. At the end of the case:
            1. Ondansetron IV 4mg
    b. **Supraoptimal prophylaxis** (5 medications)
        i. In Pre-op:
            1. Aprepitant 40mg po
            2. Dimenhydrinate (25mg) po
            3. Perphenazine 8mg po
            4. Ondansetron 4mg ODT

ii. At Induction:

1. Dexamethasone 4-5 mg IV

iii. At the end of the case:

1. Ondansetron IV 4mg

D. Variables and Compliance

a. Administration of drugs listed above

b. Rescue administration of medication for treatment of PONV in recovery room as a measure for PONV incidence via a standard protocol for all patients

i. Any antiemetic such as: dimenhydrinate, compazine, ondansetron, haloperidol, etc

c. Rescue administration of medication for treatment of PONV on hospital floor

i. Any antiemetic such as: dimenhydrinate, compazine, ondansetron, etc

E. Primary Endpoints:

a. PONV as measured by administration of PONV treatment medications after surgery

F. Goal:

a. Superiority

G. Indications for Deviation from Recommendations [2]

a. Allergy

b. Patient refusal

A3.1 References

1. Holder-Murray J, Esper SA, Boisen ML, Gealey J, Meister K, Medich DS, Subramaniam K, Korean J Anesthesiol. 2019 Aug;72(4):344-350. doi: 10.4097/kja.d.18.00355. Epub 2019 May 17.PMID: 31096730

2. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg.* 2014;118(1):85-113.

Appendix 4: Regional vs. Neuraxial Postoperative Analgesia (Arm B)

Neuraxial opioid analgesia, the administration of opioids through either the intrathecal or epidural route, can be accomplished by either a single shot (both spinal and epidural) or catheter-based therapy (epidural). The use of opioids by this route was shown to have improved pain relief when compared to preoperative oral, intravenous, or intramuscular morphine.[1] Further, neuraxial opioid analgesia is associated with lower postoperative pain scores in adults and children who undergo surgery.[2] Neuraxial analgesia can also be performed with local anesthetic only. Finally, the American Pain Society recommends the utilization of such postoperative analgesic methods in patients who undergo major surgeries, including thoracic and abdominal procedures, cesarean sections, and hip and lower-extremity surgeries; this is especially recommended for patients at risk for cardiopulmonary complications or prolonged ileus.[2]

Regional analgesic techniques such as peripheral nerve blocks, paravertebral blocks, plexus blocks, and local infiltration, can reduce postoperative physiological stress and pain.[3] These techniques have been shown to reduce the amount of opioids required for analgesia and also have been shown to reduce the adverse events seen with epidural local anesthetics (such as urinary retention and hypotension) and/or opioid containing patient controlled analgesia devices.

Traditionally, patients receive opioids during surgery, upon emergence from anesthesia when they begin to experience pain, and after surgery to treat pain.

A. Question: Is a neuraxial technique superior to a regional analgesic technique? Is the combination of neuraxial and regional analgesia techniques better than one alone?
B. Hypothesis: Preoperative neuraxial analgesia alone provides superior pain relief when compared with a regional analgesic technique alone. The combination of neuraxial and regional analgesia provides superior pain relief over either component individually.
C. Comparison/Interventions: The intervention will be prior to induction of anesthesia to provide postoperative analgesia. Patients will receive either a neuraxial morphine injection or regional technique with sodium channel nerve blockade pharmacotherapy or both.
    a. Neuraxial block:
        i. Intrathecal Morphine 150-200mcg
            1. If allergy, intrathecal dilaudid 50 – 100 mcg
    b. Regional block 1:
        i. paravertebral single shot block 20mL per side
        ii. Components of the nerve block: 0.25% Bupivacaine. Additional agents are not recommended
    c. Regional block 2:

i. quadratus lumborum 1 (QL1) single shot block 25mL per side

ii. Components of the nerve block: 0.25% bupivacaine. Additional agents are not recommended

d. Neuraxial and Regional block 1:

i. Intrathecal morphine and paravertebral single shot block

e. Neuraxial and Regional block 2:

i. Intrathecal morphine and quadratus lumborum 1 (QL1)

D. Variable and Compliance

a. Compliance defined as administration of the block

E. Primary Endpoints:

a. Oral morphine equivalents

F. Goal:

a. Superiority

G. Indications for Deviation from Recommendations[2, 4] (All therapies will comply with current American Society of Regional Anesthesia [ASRA] guidelines). All therapies are currently utilized as the standard of care.

a. Neuraxial intrathecal morphine:

i. Patients cannot receive this who have meningitis or coagulopathy, including thrombocytopenia (Platelet count < 80) or INR > 1.4.

ii. Patient refusal

iii. Allergy

b. Regional nerve blockade

i. Patients cannot receive this who have meningitis or coagulopathy, including thrombocytopenia (Platelet count < 80) or INR > 1.4.

ii. Patient refusal

iii. Allergy

A4.1 References

1. American Society of Anesthesiologists Task Force on Acute Pain M. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology.* 2012;116(2):248-273.

2. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain.* 2016;17(2):131-157.

3. De Pinto M, Dagal A, O'Donnell B, Stogicza A, Chiu S, Edwards WT. Regional anesthesia for management of acute pain in the intensive care unit. *Int J Crit Illn Inj Sci.* 2015;5(3):138-143.

4. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). *Reg Anesth Pain Med.* 2018;43(3):263-309.

Addendum 1

Due to a shortage of Aprepitant 40mg PO, the trial will be switching to Aprepitant 32mg IV until the shortage is over. Aprepitant 32mg IV is bioequivalent to Aprepitant 40mg PO. The trial uses Aprepitant 40mg PO in intervention arm B: Postoperative Nausea and Vomiting (PONV) Prophylaxis. The medication is used in the supraoptimal prophylaxis (B2) intervention recommendation. Trial participants will already have an IV for surgery; therefore, no increased risk will be placed upon the participant. Once the shortage is over, the trial will return to using Aprepitant 40mg PO. All additional uses of Aprepitant 40mg PO will be automatically substituted for Aprepitant 32mg IV systemwide during the shortage.