Domain-Specific Appendix:

Metformin

Strategies to Promote ResiliencY (SPRY)-

An Adaptive Randomized Clinical Trial of

Metformin in High Risk Surgical Patients

UPMC REMAP: Randomized, Embedded, Multifactorial Adaptive Platform Trial for Optimizing Surgical Outcomes
NCT 03861767

IRB approved January 17, 2020

Summary

In this domain of the UPMC REMAP trial, participants with elective surgery at UPMC facilities will be randomized to receive the following Metformin doses or placebo:

- Placebo
- 500mg ER daily
- 1000mg ER daily
- 1500mg ER daily

UPMC REMAP: Metformin Duration Domain Summary	
Interventions	• Placebo • 3 different doses of Metformin, • 3 different pre-operative dosing durations: short (7-28 days), intermediate (29-90 days); long (over 90 days) • Metformin continued for 90 days after surgery
Strata	Analysis and Response Adaptive Randomization are by strata (surgical type) to allow for strata-by-intervention interaction
Evaluable Interactions	Intervention-intervention interactions will be evaluated between interventions in this domain and the complimentary interventions in the ERAS Domain
Timing of Reveal	Randomization with Immediate Reveal and Delayed Initiation (with reveal and initiation only occurring after consent or agreement for participation is obtained)
Inclusions	Patients are eligible for this domain only if they have been included in the Master Protocol inclusion criteria
Domain-Specific Exclusions	Domain exclusions: • The treating clinician believes that participation in the domain would not be in the best interest of the patient • Pre-existing diabetes type I or II • Women of child-bearing potential • Presently taking metformin or prior use in the past 6 months • Evidence of an absolute or relative contraindication to Metformin therapy o Known allergy to metformin o Acute or chronic metabolic acidosis with or without coma o Hemodialysis, end-stage renal disease, or GFR < 45 in the prior 30 days o Ongoing treatment with therapy known to have significant drug-drug interaction with metformin (carbonic anhydrase inhibitors, cimetidine, gliptins) o History of lactic acidosis o History of excessive alcohol intake o Severe hepatic dysfunction
Outcome measures	Primary REMAP endpoint: hospital free days at day 90 after the surgical encounter Secondary REMAP endpoints refer to Core Protocol Secondary domain endpoints: 1. Gastrointestinal distress causing discontinuation of the medication 2. Lactic acidosis 3. Hepatic dysfunction Serious Adverse Events (SAE) as defined in CORE protocol

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1. ABBREVIATIONS

eGFR: estimated Glomerular Filtration Rate

ERAS: Enhanced Recovery after Surgery

GFR: Glomerular Filtration Rate

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and can best be described as 'modular' in its protocol design. With competing treatment interventions nested within a domain, both interventions and domains will change over time. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example, by the introduction of new domains or interventions or both and commencement of the trial in new clinics.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study) and multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain).

The Core Protocol contains all information that is generic to the trial, irrespective of the clinic in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol is void domain and intervention specifics, statistical analysis plans, and simulation specifics. The Core Protocol may be amended, but it is anticipated that such amendments will be infrequent.

Information about the intervention(s) to be examined, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each addition of a new domain and/or new intervention to an existing domain in a DSA will be subject to a separate ethics application for approval.

Although the analysis model will change over time in accordance with the domain and intervention trial adaptations, this information is contained in the Statistical Analysis and Simulations Appendices. Each modification will be subject to approval from the Trial Steering Committee (TSC) in conjunction with advice from the Data Safety and Monitoring Board (DSMB).

3. METFORMIN DOMAIN-SPECIFIC APPENDIX VERSION

The version of the Metformin Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version History

Version 1: Proposed on 16 July 2018

Version 2: Proposed on 20 January 2019

Version 3: Proposed on 25 June 2019

Version 4: Proposed on 17 July 2019

Version 5: Proposed on 31 July 2019

Version 6: Proposed on 15 October 2019

4. METFORMIN DOMAIN GOVERNANCE

4.1. Domain Members

Chair:

Derek C. Angus, MD, MPH
Professor and Chair, Critical Care Medicine
The Mitchell P. Fink Chair in Critical Care Medicine

Members:
Scott M. Berry, PhD
President and Senior Statistical Scientist
Berry Consultants LLC

Timothy Billiar, MD
George Vance Foster Professor and Chair, Department of Surgery
Distinguished Professor of Surgery
Vice-President and Chief Academic Officer, University of Pittsburgh Physicians
Associate Medical Director, UPMC International and Commercial Services Division

Philip E. Empey, PharmD, PhD
Assistant Professor
Pharmacy and Therapeutics

Stephen A. Esper, MD, MBA
Assistant Professor

Director of Perioperative Services
UPMC Department of Anesthesiology

Toren Finkel, MD, PhD
Professor of Medicine, Division of Cardiology
G. Nicholas Beckwith III and Dorothy B. Beckwith Chair in Translational Medicine
Director, Aging Institute of UPMC and Pitt

Timothy Girard, MD
Associate Professor of Critical Care Medicine
University of Pittsburgh

Jennifer M. Holder-Murray, MD, FACS
Assistant Professor of Surgery
Vice Chair for Quality Integration, Department of Surgery
Co-Director, Enhanced Recovery Program, UPMC

A. Murat Kaynar, MD, MPH
Associate Professor
Departments of Critical Care Medicine and Anesthesiology
Program Director, Anesthesiology Critical Care Medicine Fellowship

Oscar C. Marroquin, MD, FACC
Chief Clinical Analytics Officer, UPMC Health Services Division
Assistant Professor of Medicine, Epidemiology, and Clinical and Translation Sciences

Matthew D. Neal, MD FACS
Assistant Professor of Surgery and Critical Care Medicine
Attending Surgeon, Division of Trauma and Acute Care Surgery
University of Pittsburgh Medical Center

Anne B. Newman, MD, MPH
Chair, Department of Epidemiology

Katherine M. Detre Endowed Chair, Population Health Sciences
Director, Center for aging and Population Health
Professor, Epidemiology, Medicine, and Clinical and Translational Science Institute

Jeffery Romoff
President and Chief Executive Officer
UPMC

Matthew R. Rosengart, MD, MPH
Associate Professor, Surgery and Critical Care Medicine
Co-Director, Surgical Trauma Intensive Care Unit, UPMC Presbyterian

Christopher W. Seymour, MD, MSc
Assistant Professor
Departments of Critical Care and Emergency Medicine
University of Pittsburgh School of Medicine
The CRISMA Center

Jennifer Vates, MS-RA
Senior Project Manager, UPMC REMAP
Department of Critical Care Medicine

Brian Zuckerbraun, MD, FACS
Chief, Division of General/Trauma and Acute Care Surgery
Professor of Surgery

4.2. Contact Details

Jennifer Rectosh
Administrative Assistant
Trauma/General Surgery

412-692-2850

5. Metformin DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The Metformin Domain-Specific Working Group (DSWG) have read the appendix and authorize it as the official Domain-Specific Appendix for the study entitled UPMC REMAP. Signed on behalf of the committee,

Chair _____ Date _____
Dr. Derek Angus

6. BACKGROUND AND RATIONALE

6.1. Domain Definition

This is a domain within the UPMC REMAP to test the effectiveness of different doses and durations of metformin in nondiabetic patients with elective surgical encounters at UPMC who meet eligibility criteria.

6.2. Domain-specific Background

Our population is aging. Aging is associated with altered inflammatory and immune responses. This altered response has been termed “inflammaging”, and has been attributed to age-related diseases and treatment complications. Surgical stress is less well tolerated in older patients. Therapies aimed at pre-habilitation and ameliorating the response of individuals to such stressors hold the promise of improving outcomes in patients undergoing operative procedures. Pharmacological pre-habilitation possesses the potential of altering the response of older and at risk individuals towards that of younger and healthier individuals. Metformin is one such therapy based on a combination of exciting pre-clinical and clinical data demonstrating enhanced longevity and a pleiotropic modulation of inflammatory response.

6.2.1. Guideline Recommended Use of Metformin and Potential Applications

Metformin is considered first line therapy for patients with type II diabetes mellitus with hyperglycemia that cannot be controlled with lifestyle alone. Unlike other oral medications, metformin is favored for its insulin sensitizing effects resulting in improved glycemic control, weight loss, and overall improvement of metabolic syndrome. Over the past fifteen years, metformin has received significant attention for its other potential therapeutic uses and has been found to decrease the rate of age related illness progression improving longevity, especially in the setting of cancer. Additionally, recent clinical trials across multiple disease states have shown metformin to decrease all-cause mortality in diabetic and non-diabetic patients [1–3]. Although the mechanisms by which metformin affects longevity is an active area of both basic science and clinical research, it clearly has anti-inflammatory properties both independent and dependent of glycemic control [4].

6.2.2. Metformin Mechanisms of Action.

The underlying mechanisms of action of metformin are under active investigation. A leading hypothesis is that cellular mitochondria are the primary site of metformin in activity. Metformin decreases intracellular AMP and increases 5'-AMP-activated protein kinase (AMPK) resulting in three main downstream effects [2]. First and foremost, there is a decrease in gluconeogenesis, decreasing serum glucose levels, and improving insulin resistance. Secondly, mitochondrial AMPK activation inhibits mechanistic target of rapamycin (mTOR), which decreases mitotic activity and therefore has anti-tumor affects influencing mitochondrial homeostasis. Finally, downstream protein synthesis inhibition results in decreased production of both pro-inflammatory cytokines and reactive oxygen species (ROS) through activation of the thioredoxin antioxidant system decreasing DNA damage [2,4,11,12]. The anti-inflammatory effects of metformin, in addition to glycemic control, are thought to be the leading cause of the proposed anti-aging and cardiovascular protection of metformin [11]. While this clinical benefit is established in diabetic patients, the anti-inflammatory mechanism of action is, at least in part, independent of glycemic control. Therefore, as in prevention and treatment of cancer, metformin has properties that can help control inflammation in all patients with systemic inflammation.

6.2.3. Association of Metformin with Longevity in Small Clinical Trials

Recently, there have been multiple prospective clinical trials exploring the effect metformin in non-diabetic and diabetic patients. Patients were treated with standard clinical doses of metformin ranging from 250mg-2000mg three times days from 14 days to 48 weeks continuing to demonstrate an excellent safety profile. The metformin was very well tolerated with the primary side effect (30-60% of subjects) was self-limited gastrointestinal discomfort including mild diarrhea and anorexia [1,13,14]. Across multiple disease states, metformin has been shown to decrease appetite stimulating glucagon like peptide-1, decrease low density lipid profiles, decrease the mitotic rate in breast cancer, and improve liver pathology in patients with non-alcoholic steatotic hepatitis [1,3,13,15–17]. As discussed above, some of these changes are attributed to the anti-glycemic and anti-tumor effects of metformin, yet the anti-inflammatory role cannot be underestimated. However, the effects of metformin on non-diabetics and longevity remain unexplored.

6.2.4. Metformin Safety Profile

The safety profile of metformin is well established. However, there are also safety concerns regarding metformin with reports of hepatic damage and lactic acidosis, although these are

rare. More commonly, metformin can cause diarrhea and other gastrointestinal-related adverse effects, taste disturbances, headaches and muscle weakness.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of different doses and durations of metformin in select patients evaluated prior to elective surgery at UPMC.

The interventions that will be compared are:

- Varied doses of metformin (500, 1000, and 1500mg ER) started at the pre-operative clinic before elective surgical encounter at UPMC vs. placebo with continuation for 90 days post-op
- Varied pre-op duration of metformin (short-7-28 days; intermediate-29-90 days; and long-90+ days) as dictated by the individual's clinical course

We hypothesize that the elective surgical patients will experience more hospital free days at day 90 after the surgical encounter after administration of metformin vs. placebo.

We hypothesize that longer course of metformin will lead to more hospital free days at day 90 after the surgical encounter compared to a shorter course.

We hypothesize that the higher dose of metformin will lead to more hospital free days at day 90 after the surgical encounter compared to lower doses of metformin or placebo, and the effect will depend on the type of surgical procedure (and corresponding inflammatory insult). This is termed a strata-by-intervention interaction.

We hypothesize that metformin treatment will alter the complexity and diversity of the microbiome as compared to placebo (microbiome sub-study).

We hypothesize that metformin treatment will alter muscle strength as compared to placebo (Motor Assessment Group).

We hypothesize that metformin treatment will alter striated muscle fiber structure (Muscle Sub-Study) and correlate with decreased muscle strength as compared to placebo (Motor Assessment Group).

8. TRIAL DESIGN

This domain will be conducted as part of a UPMC REMAP trial for Optimizing Surgical Outcomes. Treatment allocation will be adaptive, as described in the Core Protocol.

8.1. Population

The REMAP enrolls patients with elective surgical encounters admitted to UPMC facilities. Up to 2000 patients will be enrolled.

8.2. Eligibility Criteria

Participants are included in the platform if they have all the REMAP-level inclusions and none of the REMAP-level exclusion criteria.

8.2.1. Inclusion Criteria for this Domain

Patients are eligible for this domain only if they have been scheduled for elective surgery at UPMC facilities and are being evaluated pre-operatively prior to surgery.

Other criteria include:

- Age >= 60 years
- Age < 60 but evidence of comorbidity risk as represented by a Charlson Comorbidity Index of > 2 in 12 months prior to enrollment
- Able to take an oral medication in non-crushable pill form
- Women must be post-menopausal, which is defined as not having a menstrual period within the last 12 months

8.2.2. Exclusion Criteria from this Domain

Patients will be excluded from this domain, at the time of randomization, if:

- The treating clinician believes that participation in the domain would not be in the best interest of the patient

- Pre-existing diabetes type I or II
- Women of child-bearing potential
- Presently taking metformin or prior use in the past 6 months
- Evidence of an absolute or relative contraindication to Metformin therapy
    - Known allergy to metformin
    - Acute or chronic metabolic acidosis with or without coma
    - Hemodialysis, end-stage renal disease, or GFR < 45 in the prior 30 days
    - Ongoing treatment with therapy known to have significant drug-drug interaction with metformin (carbonic anhydrase inhibitors, cimetidine, gliptins)
    - History of lactic acidosis
    - History of excessive alcohol intake
    - Severe hepatic dysfunction

8.3. Interventions

8.3.1. Research Testing and Study-related Communications

The study team may contact the patient's health care providers (including their PCP) to notify of patient's involvement in the study. These communications may occur at various times throughout the study.

8.3.2.Study Drug Intervention

Patients will be randomly assigned to intention to receive one of the following study interventions.

- Placebo
- Metformin 500mg ER
- Metformin 1000mg ER
- Metformin 1500mg ER

The dosing of and route of administration of metformin are not specified in the protocol but the following guidance is provided:

- Doses will be oral
- Subjects will be instructed to take a dose once daily and complete all dispensed medication from the provided pill bottle

Metformin should be discontinued if the patient experiences a serious adverse event (SAE) that is thought to be related to the study drug and may be discontinued at the discretion of the treating clinician if continued treatment is not in the best interest of the patient.

8.3.3. Timing of Initiation of Intervention

The intervention is to begin on the day following the evaluation of the eligible and consented subject at the pre-operative clinic/surgeon's office. Daily oral doses will continue through the hospital admission for elective surgery. For patients without side effects, dosing will continue daily for 90 days after the surgical encounter.

Patients will be contacted between the pre-operative clinic/surgeon's office visit and surgery to evaluate study drug compliance as well as any adverse events associated with the study drug.

8.3.4. Duration of Administration of Study Drug

The duration of Metformin therapy is a complimentary research question in this domain. In the short course intervention, subjects will receive the study drug (metformin or placebo) within 7-28 days prior to the elective surgical encounter. In the intermediate course therapy, subjects will receive the study drug for 29-90 days prior to surgery. In the long course therapy, patients receive a longer course of study drug prior to surgery when the pre-operative evaluation occurs far enough in advance (e.g., >3 month). All patients will receive study drug for 90 days after the surgical encounter.

8.3.5. Temporary Suspension of Study Drug

If the patient should experience any of the following, study drug administration will be temporarily discontinued for 48 hours:

- Procedure involving the administration of contrast dye

8.3.6. Suspension of Study Drug at the Direction of the Treating Clinician

Study drug administration may be suspended at the direction of the treating clinician in the event a patient should experience a medical condition where it is felt there is a predisposition to renal impairment and/or tissue hypoxia.

8.3.7. Collection of Blood Samples

As part of this domain, blood samples may be collected over the course of a patient's participation in this domain. These blood samples will be processed and aliquoted for long-term storage in a biorepository which will permit the analysis of such aliquots at a future unspecified date. Collection of blood samples from patients participating in this domain will be attempted at the following timepoints:

- Pre-op clinic visit
- Day of surgery (often in pre-op holding area)
- After surgery
- Post-op Day 3 or immediately prior to hospital discharge if sooner
- Post-op clinic visit

Where possible, blood samples will be piggy-backed at the time of clinical draws or will be taken through established intravenous lines to minimize patient discomfort. If there is concern the collection of blood samples via the established intravenous line may jeopardize the patency of this line, the blood sample may be drawn directly from a patient's vein. Blood samples will be processed via standard operating procedures and aliquoted to permit long-term storage. These blood samples will be maintained by the Department of Critical Care Medicine for an indefinite period of time. Each aliquot will bear a unique code number which will permit matching to coded medical record information, while guarding patient identity. Aliquots may be used by investigators within the University of Pittsburgh/UPMC as well as by external investigators. Any request for the use of aliquots banked in the biorepository will need to be reviewed and approved by the Biorepository Steering Committee.

8.3.8. Collection of Samples for Microbiome Sub-study

There is interest to determine how the microbiome may change over the course of this study. For this reason, up to 1000 subjects participating in this domain may be asked to participate in a microbiome sub-study. This sub-study will attempt to collect stool samples of participants at 3 timepoints:

- prior to surgery
- during the inpatient hospital admission or following hospital discharge and within 5 days of surgery
- temporal to the post-op visit

Those stool samples collected prior to and after the inpatient hospital admission should be returned to study personnel via pre-paid mailing envelopes. Subjects participating in the microbiome sub-study may also undergo a rectal swab on the day of surgery.

8.3.9. Collection of questionnaires

To examine cognitive and/or motor changes over the course of the study, subjects may complete a series of questionnaires. All subjects participating in this domain will be scheduled to have questionnaires completed via telephone interaction prior to their surgery and 30 days (+/- 7 days) after their index surgery.

The following questionnaires should be completed during the telephone call prior to the index surgery:

- EQ-5D (quality of life)
- MoCA-BLIND
- Functional Activities Questionnaires (FAQ)

The following questionnaires should be completed during the 30-day telephone call:

- Post-discharge resource use questionnaire
- EQ-5D (quality of life)
- Return to work questionnaire

In order to assess motor function, up to 1/3 of subjects who are over the age of 65 and living within 20 miles of the primary research offices may be asked to attend a 90 day (+ 28 day) in-person visit (Motor Assessment Group). This visit should include questionnaires similar to those completed during the 30-day telephone call as well as motor assessments, specifically:

- Post-discharge resource use questionnaire
- EQ-5D (quality of life)
- Return to work questionnaire
- Functional Activities Questionnaires (FAQ)
- NIH Toolbox
    - Cognition Battery
    - 2 Minute Walk Test
    - Grip Strength

On a case-by-case basis, the study team may determine it best to collect these questionnaires via telephone interaction.

For those subjects who do not attend the 90 day in-person visit, the following questionnaires will be completed via telephone interaction at 90 days post-op (+ 28 days):

- Hospital readmission questionnaire (primary endpoint)
- EQ-5D (quality of life)
- Return to work questionnaire
- Functional Activities Questionnaires (FAQ)
- Cognitive battery (MoCA-BLIND, Hayling, and phone CAM)

To avoid in-study learning by patients, alternative versions will be administered for those questionnaires used at multiple timepoints.

If someone should indicate by their answer on the EQ-5D that they are extremely anxious or depressed, a member of the LTOC team will ask if the subject has discussed these feelings with their health care providers. If yes, no further action is taken.

Regarding monitoring for anxiety or depression in subjects as per the queries on the interviews, if the patient answers no, then a written communication would be sent to the patient's PCP and surgeon for the SPRY-related procedure to communicate the subject's 'feeling extremely anxious or depressed' response on the EQ-5D, the context of the EQ-5D administration (that is, administered in conjunction with a research study). The PI and study team would also be notified of the patient's response.

8.3.10. Muscle Biopsy Sub-Study

In collaboration with Dr. Micah Drummond of the University of Utah, who focuses his research on the cellular and molecular mechanisms of muscle growth, we intend to explore Metformin's effect on striated muscle growth and structure. Muscle atrophy is a common occurrence within an aged population, often attributed to the decreased mobility and disuse seen in older adults. This finding may be accelerated after surgery and prolonged immobility. Dr. Drummond is currently investigating as part of a randomized clinical trial whether Metformin may mitigate muscle atrophy through its ability to improve insulin sensitivity via AMPK pathway blockade. Dr. Drummond's clinical trial[18] compares metformin to placebo for individuals on bed rest for five consecutive days.

All subjects from the Motor Assessment Group who are willing are eligible for the Microbiome and Muscle Biopsy Sub-studies. We intend to expand upon Dr. Drummond's work by enrolling up to 200 subjects from the SPRY study to assess the potential effect of Metformin on striated muscle tissue structure. This will be particularly relevant to assess in our patient cohort who are at risk for accelerated muscle atrophy after surgical stress. Subjects involved in this sub-study may have up to 2 muscle biopsy samples taken at 2 separate timepoints- on the day of elective surgery while the patient is under anesthesia and during the Visit at 90 days (+ 28 days) after surgery following the administration of lidocaine. The 90-day muscle biopsy will occur in either the Radiology Procedure Unit B or on the 8th floor of Montefiore Hospital.

Determining Metformin's effect on muscle tissue may be evaluated by measuring muscle fiber cross sectional area and correlating to muscle strength. In addition, the myogenic potential of sample myotubes may be evaluated.

In addition, as changes in muscle mitochondrial respiration are often seen with muscle atrophy, there is interest to examine this aspect and Metformin's potential effect.

To further examine this aspect, Drs. Forman, Newman, and Finkel would like to be able to retain some of the above-referenced samples from the up to 200 subjects from whom muscle biopsies are obtained to investigate questions related to mitochondrial respiration using fresh muscle tissue as well as to use frozen tissue for questions about lipid and protein metabolism.

Muscle biopsies will be performed by physicians on the study team experienced in muscle biopsies, specifically Drs. Neal, Rosengart, Zuckerbraun, and Forman.

The muscle sample collection procedure involves using a needle to take a small piece of muscle tissue from the outside of the patient's upper leg, about 4-6 inches above the knee. Following cleaning of the skin, Lidocaine will be injected to minimize any pain. A small incision about the size of this dash "__" (1/4th of an inch) will be made in the skin, through which a needle about the size of the letter "O" is slowly inserted into the muscle. A piece of the muscle (0.125-0.5 gram) is then removed with the needle, the skin is closed with a steri-strip and a light dressing is applied then a pressure wrap is placed over the dressing.

For patients involved in the Muscle Biopsy Sub-Study, anti-coagulant medications will be held per their standard of care pre-op directions for the biopsy conducted on the day of surgery. For the 90-day muscle biopsy, patients will be advised to hold:

1.Apixaban, Rivaroxaban, Dabigatran, Edoxaban (also known as Eliquis, Xarelto, Pradaxa, Savaysa)—48 hours

2. Aspirin, coated or uncoated (also known as Bayer, Bufferin, Exedrin, Ecotrin, Ascriptin)---5 days

3. Clopidogrel, Ticgrelor, or Pragruel (also known as Plavix, Brilinta, Effient)---5 days

4. Warfarin (also known as Coumadin)---5 days

5. Aggrenox (also known as Dipyridamole and Persantine)---5 days

6. Ticlid (also known as Ticlopidine)---5 days

7. Agrylin or Xagrid (also known as Anagrelide)---5 days

The study team will confirm the patient has held these medications prior to performing the muscle biopsy.

Appropriate post-biopsy care instructions will be provided to patients and a contact person in case they experience signs or symptoms of concern.

The study team will also assure patients receive post-op care instructions from the clinical team as need per their surgery and length of stay.

For both biopsies timepoints, technicians working under the direction of the study team will process the specimens. Some of these muscle samples (or a portion of the sample) may be retained for local use and storage while the remainder of the samples may be analyzed by collaborators such as the University of Utah. These technicians will be responsible for the processing of tissue for local use as well as for the shipping of shipping of the frozen muscle biopsy samples and associated research data to collaborators such as the University of Utah, an identified collaborator, in batches. Dr. Drummond will not store this tissue for long-term use.

8.4. Endpoints

8.4.1. Primary Endpoint

The primary endpoint for this domain is the REMAP primary outcome of hospital free days at 90 days after the elective surgical encounter.

8.4.2. Secondary Endpoints

All secondary endpoints as specified in the Core Protocol.

The domain-specific secondary outcome measures (occurring during the index elective surgical procedure), include:

- Hypoglycemia
- Gastrointestinal intolerance
- SAE as defined in Core Protocol
- 1 year mortality

9. TRIAL CONDUCT

9.1. Domain-specific Data Collection

9.1.1. Clinical Data Collection

Patients who are randomized in this domain will have the following data collected:

- Treatment allocation at the time of enrollment
- Successful dispensing of study medication
- Gastrointestinal intolerance
- SAE as defined in Core Protocol

9.2. Criteria for Discontinuation

Refer to Core Protocol for discontinuation criteria for the participation in UPMC REMAP.

9.3. Blinding

9.3.1. Blinding

We will attempt blinding in the following ways. All medication tablets will be void of dosage amounts or stamps that identify dose. Each patient will have the number of pills appropriate to the dose to which they are randomized. For placebo patients, we will randomly select whether they receive 1, 2, or 3 tablets, all of which will be placebo. Placebo pills will appear identical to study drug in color, size, shape, and markings, to the extent legally possible.

9.3.2. Unblinding

N/A

10. STATISTICAL CONSIDERATIONS

10.1. Domain-specific Stopping Rules

If a Platform Conclusion (as defined in the Core Protocol) of equivalence in the primary endpoint is demonstrated, the DSMB and the TSC may consider continuation of randomization if clinically relevant differences in secondary endpoints have not been demonstrated and it is considered

plausible that clinically relevant differences in one or more secondary endpoints may be capable of being demonstrated. In all other respects, the stopping rules for this domain are those outlined in the Core Protocol.

In general, the following futility stopping rules shall apply to this domain:

- Drop dose t within duration k if the probability that it is better than placebo by clinically significant difference (OR of .8) is less than 15%: Pr(e^(γ_(k,t))<.8)<.15
- Stop enrolling to duration k if all doses have been dropped in that duration
- Stop domain for futility if all doses/durations have been stopped

The following rules shall apply to define success stopping for this domain:

- Pool all active enrolling durations within each dose. Estimate pooled effect within each dose.
- Posterior Probability Best Dose is better than placebo > Success threshold
- Success threshold is based on O'Brien Fleming stopping bounds and multiplicity correction for 3 doses.

More detailed stopping rules may be found in the Statistical Analysis Plan associated with the Core Protocol.

10.2. Strata

Both analysis of the treatment effect and the Response Adaptive Randomization (RAR) will utilize the stratum of surgical clinics in this domain.

10.3. Timing of Revealing of Randomization Status

The revealing of allocation status and administration of interventions is not specified to occur during the trial.

10.4. Interactions with Interventions in Other Domains

An *a priori* interaction with the ERAS Domain is considered possible and will be incorporated into the statistical models used to analyze this domain.

10.5. Post-trial Sub-groups

Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The *a priori* sub-groups of interest include:

- Patients eligible due to comorbidity (and not age criteria)
- Pre-operative exposure duration anticipated to be (eg. <28, 29-90, >90 days)
- Surgical procedure type

11. ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, inferiority, or equivalence of different interventions with respect to the primary endpoint is possible, and if equivalence is demonstrated, the optimal treatment may be based on secondary endpoints.

11.2. Potential Domain-specific Adverse Events

The drug used in this domain has a known toxicity profile and adverse events are rare.

Domain-specific harms related to metformin include:

- Gastrointestinal intolerance
- Hypersensitivity
- Lactic acidosis
- Hemolytic anemia
- Malabsorption

11.3. Domain-specific Consent Issues

Metformin is approved and is in common use in many countries.

The use of prolonged courses of metformin is widely used for diabetes and the doses proposed in this trial are well within the standard range. Clinics will be able to opt out of this domain for all patients at that site if they believe that this intervention is not part of reasonable care of patients

evaluated for elective surgery. Additionally, clinicians may choose not to enroll individual patients if they feel that participation is not the patient's best interests.

12.GOVERNANCE ISSUES

12.1. Funding of Domain

The SPRY trial is funded by UPMC.

12.2. Domain-specific Declarations of Interest

All investigators involved in UPMC REMAP will maintain a registry of interests with UPMC. These are updated periodically and publicly accessible on the study website.

13.REFERENCES

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