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Strategies to Promote ResiliencY (SPRY): A Randomized Embedded Multifactorial Adaptative Platform (REMAP) Clinical Trial Protocol to Study Interventions to Improve Recovery after Surgery in High Risk Patients

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Abstract

Introduction: As the population ages, there is interest in strategies to promote resiliency, especially for frail patients at risk of its complications. The physiologic stress of surgery in high risk individuals has been proposed both as an important cause of accelerated age-related decline in health and as a model testing the effectiveness of strategies to improve resiliency to age-related health decline. We describe a randomized, embedded, multifactorial, adaptative platform (REMAP) trial to investigate multiple perioperative interventions, the first of which is metformin and selected for its anti-inflammatory and anti-aging properties beyond its traditional blood glucose control features.

Methods and analysis: Within a multi-hospital, single healthcare system, the Core Protocol for Strategies to Promote ResiliencY (SPRY) will be embedded within both the electronic health record (EHR) and healthcare culture generating a continuously self-learning healthcare system. Embedding reduces the administrative burden of a traditional trial while accessing and rapidly analyzing routine patientcare EHR data. SPRY-Metformin is a placebo-controlled trial, and the first SPRY domain evaluating the effectiveness of 3 metformin dosages across 3 preoperative durations within a heterogeneous set of major surgical procedures. The primary outcome is 90-day hospital free days. Bayesian posterior probabilities guide interim decision making with predefined rules to determine stopping for futility or superior dosing selection. Using response adaptative randomization, a maximum of 2,500 patients allows 77% to 92% power, detecting >15% primary outcome improvement. Secondary outcomes include mortality, readmission, and postoperative complications. A subset of patients will be selected for substudies evaluating the microbiome, cognition, postoperative delirium, and strength.

SPRY-Metformin Protocol

Ethics and dissemination: The Core Protocol of SPRY REMAP and associated SPRY-Metformin Domain-specific Appendix have been ethically approved by the Institutional Review Board and are publicly registered. Results will be publicly available to healthcare providers, patients, and trial participants following achieving predetermined platform conclusions.

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Article Summary

Article focus

- A randomized, embedded, multifactorial, adaptative platform (REMAP) trial efficiently evaluating the effectiveness of perioperative therapies in aged, frail patients (Strategies to Promote ResiliencY [SPRY]) for which the physiologic stress of surgery is a cause of physiologic age-acceleration and can result in significant morbidity and mortality.
- Metformin has pleiotropic anti-inflammatory properties potentially slowing the process of aging and improve perioperative outcomes in non-diabetics and will be the first domain to be tested on the SPRY Core Protocol (SPRY-Metformin).

Key message

- The electronic health record embedded SPRY-Application, synchronizes trial activities into standard of perioperative care, minimizes both the administrative burden and costs associated and allows for rapid Bayesian adaptative analysis minimizing harm to enrolled and future patients and establishing an effective treatment strategy.

Strengths and Limitations

- Trial protocol embedded within the electronic health record using a REMAP design with concurrent biorepository (i.e., blood and stool) sample collection.
- Outcome information may be limited or incomplete in patients who receive postoperative care within the multi-hospital healthcare system.

Keywords

Randomized embedded multifactorial adaptive platform, REMAP, metformin, 90-day hospital free days, perioperative optimization, aging, prehabilitation

Introduction

By 2020, over 55,000 Americans will be greater than 65 years of age [1]. The lifelong accumulation of stressors progressively leads to chronic disease and disability compromising homeostatic reserve. These health deficits, defined as frailty, leave individuals vulnerable to a physiologic insult further reducing resiliency [2]. In response, a broad range of multimodal therapies (e.g., smoking cessation, nutritional optimization, physical activity programs, etc.) are currently under investigation to both prevent and reduce the effects of aging [3]. However, as frailty is developed longitudinally, establishing treatment efficacy in clinical trials requires years to decades of outcome monitoring [4].

A lifetime of exposure to multiple, small stressors may cumulatively reduce reserve equal to that of few, severe stressors [5]. Elderly patients undergo over one third of all surgical interventions and have an increased rate of postoperative morbidity and mortality [5–8]. According to the National Institute for Aging, the severe stress of a surgery is an "age-accelerating" cause of frailty [5], rapidly depleting resilience to secondary insults [9,10]. Therefore, a major surgical intervention is an efficient experimental model for evaluating novel strategies aimed at stabilizing, preventing, or reversing frailty [5].

Perioperative investigations strive to improve outcomes in an aged and at-risk population and also model accelerated aging. We have therefore designed a randomized, embedded, multifactorial, adaptative platform (REMAP) [11] trial to evaluate the effectiveness of perioperative therapies within a multi-hospital single healthcare system: Strategies to Promote ResiliencY (SPRY). Metformin, the most commonly prescribed non-insulin medication for those with diabetes [12–14], has pleiotropic anti-inflammatory properties, and potentially slows the process of aging [15,16]. Therefore, we report the first of many trial protocols evaluating perioperative therapies on this adaptive platform, SPRY-Metformin, randomizing patients to 3 dosages of metformin or placebo in parallel.

Methods and Analysis

Aims

The primary aim of SPRY is to establish the Core Protocol infrastructure for continuous and simultaneous adaptive analysis of multifactorial perioperative therapies evaluating their effect on resiliency to age-accelerating surgical stress in patients at risk for postoperative morbidity and mortality.

The primary aim of the SPRY-Metformin domain is to establish the ideal duration and dose of perioperative metformin to determine its effectiveness as pharmacologic optimization across multiple surgical specialties.

Unified, the aims of the Core Protocol and all associated multifactorial Domain-specific Appendixes are to embed the study protocols both digitally within the electronic health record (EHR) and culturally among clinicians generating an efficient, cost-effective, patient centered and continuously self-learning healthcare system.

Trial Design

The design of the SPRY Core Protocol and associated Domain-Specific Appendices align with the recommendations of the Adaptive Platform Trials Coalition [17] and SPIRIT guidelines [18]. Specifically, SPRY will perpetually assess multiple treatments in multiple surgical and disease subtypes using response adaptive randomization and a comprehensive statistical analysis plan to create a self-learning health system. The protocol underwent prelaunch regulatory, scientific, and ethical review and all results will be reported based upon the trigger of formal stopping rules.

Patient and Public Involvement

No patient involvement.

SPRY-Metformin Protocol

SPRY *Core Protocol*

SPRY is the first Core Protocol outlining the embedding of a trial within the EHR and routine perioperative healthcare delivery for at-risk, aged adults. The Core Protocol creates standardized trial elements shared by all applied trials or domains preventing the continuous development and then dismantling of the expensive and complex clinical trial infrastructure [19]. As with other adaptive platform trials, SPRY assesses multiple interventions simultaneously using Bayesian statistical analysis and response adaptive randomization evaluating the treatment effect in predefined surgical specialties (e.g., vascular, orthopedics, spine, hepatobiliary, etc.) or strata [20,21]. In the REMAP design, patients can be randomized to one of many treatments within one of many domains resulting in multiple possible experimental treatment combinations. The Core Protocol allows for aggregation of the treatment response across different domains and the multifactorial evaluation of synergistic or antagonistic combinations within each of the strata.

SPRY trial flow per the Consolidation Standard of Reporting Trials (CONSORT) guidelines are adapted from the traditional linear format into a concentric diagram, demonstrating the perpetual nature of the Core Protocol (**Figure 1A**).

SPRY-Metformin Domain-Specific Appendix

SPRY-Metformin is a multi-hospital, single healthcare system, placebo-controlled, adaptive, phase 3 clinical trial that is blinded at the level of the patient, clinician, research team, and data analyst. SPRY-Metformin is the first domain to be launched on the SPRY Core Protocol testing the effectiveness of metformin in improving perioperative outcomes (**Figure 1B**). Patients are screened and recruited through a custom EHR embedded application (**Figure 2**). Enrollment, consent, and study drug dose randomization occur within standard of care preoperative surgical and anesthesia clinic appointments at contact point 1. In the following 7 to 180 days, patients

are pragmatically assigned to 1 of 3 preoperative study drug durations (short, intermediate, or long) based upon the scheduled date of their elective, major surgical intervention. Patients undergo an operation (contact point 3) and study drug is continued throughout the perioperative period through postoperative day (POD) 90 (**Figure 3**). All patients are prospectively monitored through POD 365 through both the automated collection of EHR data and longitudinal patient follow up (contact point 2, 5, 6).

Trial Embedding

The integration of this trial into the EHR and clinical workflow requires two distinct forms of embedding: digital and cultural.

Digital Embedding

We developed Java-based (Oracle Corporation, Redwood Shores, CA) custom software, the SPRY-Application, which interfaces with the research team and EHR. The digital embedding of the SPRY-Application serves multiple purposes. First, protecting the privacy of trial patients. Second, automating patient screening, enrollment, and randomization while synchronizing research activities within perioperative standard of care clinical encounters. Third, accessing the robust EHR data generated as a part of routine patient care.

At UPMC, a two-factor authentication system safeguards all private patient information accessed through a single Citrix Workspace (Fort Lauderdale, FL) in accordance with Health Insurance Portability and Accountability Act. Like all protected data and programs within the healthcare system, the SPRY-Application resides behind this institutional firewall. Here, the SPRY-Application is distinct from, but communicates with the inpatient (CERNER Co., Kansas City, MO) and outpatient (Epic Systems Co., Madison, WI) EHR, subject to the security measures protecting UPMC patient privacy.

The SPRY-Application screens each patient with a scheduled appointment at enrolling preoperative SPRY-Metformin clinics (**Figure 3**). The EHR of each scheduled patient is reviewed, generating a list of patients meeting a subset of inclusion and exclusion criteria. This list of potential SPRY-Metformin candidates is then automatically distributed to the clinicians via institutional email.

In preoperative clinics, patients are offered the opportunity to participate in SPRY-Metformin. The SPRY-Application guides the surgeons and anesthesiologists through the stepwise informed consent process. Then, EHR data auto-populate patient specific screening information within the SPRY-Application, which are then reviewed and confirmed with the patient. Any discrepancies between patient report and the EHR auto-populated SPRY-Application data prompt the clinician to update the EHR (**Figure 1A**). This both minimizes trial data entry and maintains the accuracy of clinical information.

Patients meeting all inclusion and no exclusion criteria are randomized based upon the SPRY-Application algorithms accounting for the preoperative duration, enrolling site, age (e.g., <75 or $\geq$ 75), and surgical strata. Automatically, the SPRY-Application then generates the study drug and laboratory prescription and synchronizes all research activities (e.g., blood and stool samples) within pertinent perioperative standard of care clinical encounters. The SPRY-Application monitors for Cerner Admission-Discharge-Transfer alerts and informs the research team of hospital admissions and discharges for enrolled patients. Inevitable in-trial schedule changes can be manually updated within the SPRY-Application adjusting the research activity timeline, updating research personnel, and distributing additional study drug, as needed, via the mail.

Predefined clinical care information recorded within the EHR is abstracted by the SPRY-App via SQL Server. Like the SPRY-Application and EHR, these data are stored behind the UPMC firewall and managed by Biostatistical and Data Management Core in the Department of Critical Care Medicine at UPMC.

Cultural Embedding

SPRY-Metformin is designed with the intent to rely heavily on bedside clinicians for many aspects of trial execution. Healthcare system staff within high volume surgical clinics are busy with existing patient care responsibilities. We have attempted to minimize the burden of research in two ways. First, whenever possible, the protocol is fused within existing care activities. Second, we focus on engaging, educating, and motivating the entire clinical team.

For example, as each new site is identified, prior to site initiation, the research team informs the clinical team about the potential benefits of a REMAP trial design and a self-learning healthcare system. Simultaneously, the clinical team educates the research team on their patients' experiences and the clinic or unit specific workflow. Both teams then work together to generate both clinic or unit specific protocols and SPRY-Application user manuals.

Embedding minimizes the time required by each individual clinician and researcher by distributing the research effort across many capable hands, guided by the SPRY-Application.

Study Population

The evaluation of enrollment criteria for the study population occurs across two formats and at two levels. Initially, a subset of criteria is screened digitally by the SPRY-Application. Subsequently, in clinic the consenting clinician confirms all inclusion and exclusion criteria. As prompted by the SPRY-Application, any discrepancies found between the data within the SPRY-Application and the patients' reported health state are manually updated within the SPRY-Application and EHR (**Figure 4**).

At the first level, participants must meet all SPRY inclusion and no exclusion criteria. At the second level, participants are evaluated against the inclusion and exclusion criteria of the SPRY-Metformin domain (**Table 1**). Patients randomized in SPRY-Metformin can also

participate in either or both substudies (microbiome or motor) as well as additional future domains on the SPRY Core Protocol.

SPRY-Metformin Intervention

Metformin Rationale

We hypothesize that pharmacologic perioperative optimization will improve surgical outcomes for an aged, frail patient population. Metformin, the most commonly prescribed non-insulin medication for type 2 diabetics, is one such therapy [12–14]. In multiple studies, metformin consistently delays the aging process and minimizes deleterious cellular inflammation [4] through effects on cellular respiration [22], muscle function [23], and the microbiome [24]. Metformin advantageously modulates the body's response to physical stress through its systemic anti-inflammatory properties [25,26]. These biologic mechanisms and pleiotropic effects appear to be independent of blood glucose control [26].

Metformin has an excellent safety profile and is well tolerated [12–14]. Traditionally in diabetics, metformin is discontinued throughout the perioperative period because of both potential hypoglycemia and the theoretical risk of metabolic induced lactic acidosis. As monotherapy, metformin is not expected to cause hypoglycemia [13]. Multiple cohort studies and meta-analysis have demonstrated the risk of metabolic acidosis to diabetics is not higher in those prescribed metformin [27]. Therefore, there is no expected risk of metformin induced lactic acidosis in those with adequate screening renal and hepatic function [27,28]. Therefore, perioperative metformin is the first optimization strategy to be tested on the SPRY Core Protocol.

Study Drug

Both the duration and dose of study drug exposure will be evaluated. Patients are stratified based upon the anticipated perioperative duration: short (7-28 days), intermediate (29-90 days),

or long (91-180 days). Within each duration window, patients are randomized to 1 of 3 doses of metformin extended release 500, 1000, or 1500mg, or placebo. Patients allocated to the 1500mg arm are prescribed 2 500mg tablets for 7 days before ramping up to the full 3 tablet dose [29]. In the placebo arm, the same ramp up procedure and multiple dosages are used maintaining the blinded nature of this study.

Study drug is initiated the day following randomization and continued through postoperative day 90 without planned interruption perioperatively. Patients compliance is queried at follow up patient encounters (**Table 3, Figure 2**).

EHR Embedded Safety Alerts

Surgical stress can cause fluctuation in organ function perioperatively. As a part of routine clinical care, patients at the greatest risk of physiologic derailment and significant postoperative complications in the postoperative period are admitted for monitoring. Therefore, the SPRY-Application monitors the results of postoperative renal and hepatic testing completed as a part of routine postoperative care. Both evidence of current (i.e., estimated glomerular filtration rate <45 or serum lactate ≥ 4) or potential future (i.e., ordered contrasted imaging studies) organ dysfunction generate “pop-up” style CERNER EHR alerts prompting the bedside nurse to hold study drug administration (**Figure 2**). Simultaneously, an institutional email notifies the research team facilitating clinical to research physician consultation.

Endpoints

The primary endpoint of SPRY Core Protocol is the number of hospital free days (HFD) up to 90 days [30–33]. This composite endpoint is an ordered categorical variable defined as the number of days from the day of surgery to the 90 thereafter, during which the patient is alive and free of hospitalization. If a patient is discharged and readmitted, then this hospital exposure is added to

the duration of the primary admission. Hospitalizations within the healthcare system are monitored and recorded by the EHR embedded SPRY-Application. Out of system hospitalizations are reviewed at each postoperative point of contact (2, 5, 6; **Figure 3**). Emergency department and unplanned outpatient evaluations without admissions are not included in this composite. Any person who dies within this 90-day period is assigned -1 HFD, even if there is a period during which the patient is not within the hospital. Thus, mortality is specifically captured and this endpoint reflects the recovery for high-risk patients following a major surgical intervention.

The predefined and validated secondary clinical endpoints are listed in **Table 2** and **Table 3** [34–37]**.** All within healthcare system outcomes (i.e., intensive care admission and duration; organ failure free days; in-hospital mortality; hospital discharge location; and reoperation and readmission rates) are automatically abstracted from the EHR. Other outcomes (i.e., surgical site infection [35] and occurrence [36], deep vein thrombosis and pulmonary embolism rates) are manually abstracted from the EHR. Out of healthcare system outcome in addition to quality of life [38], cognitive [39–41], delirium [42], functional testing [39,43], and employment status are monitored prospectively with further physiologic testing [44,45] for those in the motor substudy (**Table 3, Figure 3**).

Biorepository

An additional long-term goal of SPRY-Metformin is to understand the molecular mechanisms by which metformin might attenuate the inflammatory response and improve outcomes after surgical stress. In order to provide a library for future biological testing and sampling, SPRY-Metformin is creating a biorepository including a maximum of 5 blood samples (contact points 1, 3 [POD 0-3], and 4) throughout the trial (**Figure 3**). Patients discharged prior to POD 3 will have the fourth blood sample collected only if a venous blood sample is clinically indicated on the day of discharge. The biorepository includes the collection of peripheral blood mononuclear cells,

plasma, and planned collections for DNA, RNA, and metabolomic analysis. Substudy patients will provide additional biorepository samples: microbiome (stool samples contact point 2, 3 [intraoperative rectal swab], 4, and 5) and muscle biopsy (contact point 3 [intraoperative] and contact point 6). Microbiome samples will be captured and preserved with the Zymo DNA/RNA Fecal Collection Kit (Zymo Research, Irvine, CA).

Statistical Analysis

Complete documentation of the statistical analysis plan is including as supplemental materials.

Simulations and Sample Size Generation

In collaboration with Berry Consultants, LLC trial simulations quantified operating characteristics of the SPRY-Metformin trial. Utilizing retrospective UPMC EHR data, virtual patient datasets were created based on the observed distributions of the primary endpoint within each stratum. Patients randomized to placebo were simulated according to the observed HFD distributions conditional on the assumed surgical strata of the patient. Patients randomized to active treatment were simulated assuming a common percent increase in HFD days across all strata between 0% (null) and 15% (alternative) for the highest dose of the treatment. Under each treatment effect assumption, many trials were simulated and virtually executed, including all interim analyses and adaptations. Trial behavior, such as power and type I error were summarized as the proportion of simulated trials that were successful under the alternative and null scenarios respectively.

Patients will be adaptively randomized to placebo or 3 doses of metformin, the trial has at least 84% power to detect a treatment effect of at least a 15% reduction in mean hospital days for a minimum of 1 of the doses under the assumption that the dose is equally effective across all 3 preoperative metformin durations. If a dose is not effective for the short preoperative

duration, the trial has at least 77% power to detect a treatment effect of at least a 15% reduction in mean hospital days for at least 1 of the doses.

The motor subgroup will enroll up to one third of SPRY-Metformin trial patients. The microbiome and muscle biopsy subgroups are exploratory pilot substudies with 1,000 and 200 patients to be enrolled respectively.

Response Adaptative Randomization and Interim Analysis

Initially, SPRY-Metformin will randomize a maximum of 2,000 patients. Within each of the 3 preoperative durations, patients will initially be randomized $\sqrt{3}$:1:1:1 to placebo and the 3 doses of metformin. Interim analysis is completed each time 500 patients have been randomized across all preoperative durations and followed for 90 POD. At each interim analysis, the trial can be stopped early for demonstrating efficacy on any one of the metformin doses compared to placebo. If the trial has not stopped for success, the response adaptative randomization will preferentially randomize to the best performing metformin doses within each preoperative duration while maintaining the allocation to placebo. If there is a low posterior probability of efficacy (odds ratio, OR $\leq$ 0.8), single or multiple doses can be dropped for futility. If all doses have been dropped within a preoperative duration, enrollment to that preoperative duration will be stopped. Finally, the maximum sample size will be increased from 2,000 to 2,500 if at least one dose within one preoperative duration has $\geq$ 50% posterior probability of efficacy (OR $\leq$ 0.8).

The interim analyses and all resulting actions including updates to randomization probabilities are pre-specified and not subject to recommendations from the Data Safety and Monitoring Boards (DSMB). However, the DSMB may make recommendations regarding safety, trial conduct, or ongoing scientific validity, integrity, and both clinical and scientific relevance of the study.

SPRY-Metformin Protocol

Analysis Plan

The primary analysis method of 90-day HFD within SPRY-Metformin is a Bayesian ordinal logistic regression model that accounts for differences in the expected 90-day HFD distribution depending on surgical strata. Within this model, the effect of each dose of metformin for each preoperative duration relative to placebo is characterized as a constant log-OR shift in the 90-day HFD distribution. The primary intention to treat analysis will include those who have been randomized. All missing data will be imputed based upon the median observed 90-day HFD value for each treatment arm and preoperative duration. Sensitivity analysis may explore a per protocol analysis and alterative imputation strategies.

Superiority of a metformin dose to placebo within SPRY-Metformin is determined based on the posterior probability that the pooled log-OR effect of that dose across all enrolling preoperative durations relative to placebo is less than 0, indicating a shift in the 90-day HFD distribution towards more HFD under treatment compared to placebo. Success is declared at an interim or at the final analysis if the posterior probability of superiority for any dose of metformin is greater than the pre-defined interim-specific success threshold. The thresholds are based on an O'Brien Fleming spending function assuming a maximum sample size of 2,500 [46].

SPRY-Metformin secondary outcomes will be analyzed using regression models that account for expected differences in surgical strata of the patient (**Table 2, 3**).

Additional domains and additional interventions within domains will be added to the SPRY Core Protocol. Treatment effects can be added for each additional perioperative therapy, as well as treatment-by-subgroup interactions to evaluate the heterogeneity of treatment effects between the existing SPRY-Metformin and future domains.

Ethics and Dissemination

SPRY-Metformin Protocol

Both the Core Protocol and SPRY-Metformin Domain-specific Appendix were independently approved at the University of Pittsburgh Institutional Review Board (IRB# 18060039, 18060038) without a required Investigational New Drug exemption from the Food and Drug Administration. Three independent groups were established to provide oversight for SPRY-Metformin: Trial Steering Committee (TSC), Statistical Monitoring Committee (SMC), and DSMB. The blinded TSC oversees the overall trial conduct and makes recommendations regarding all trial-related decisions. The unblinded statisticians of the SMC are responsible for conducting and monitoring the interim analyses reporting patient enrollment, patient status, and a summary of trial adaptations based upon the pre-specified protocol.

The DSMB reviews patient safety and protocol compliance reports generated by the SMC [47] and makes trial conduct recommendations to the TSC (**Figure 4**).

Platform conclusion

In SPRY, a platform conclusion describes when a statistical trigger has been reached and, following evaluation by the DSMB and in conjunction with the TSC, a decision is made to conclude a domain or intervention within a domain for superiority, equivalence, or futility. Under all circumstances, a platform conclusion leads to implementation of the result within the REMAP and under almost all circumstances a platform conclusion leads immediately to Public Disclosure of the result by presentation and publication by the SPRY research team.

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Declarations

Author Statement

KR, CS, JV, OM, SE, JH, SB, DA, and MN participated in the creation of the study concept, protocol implementation, and outcome selection. JV, CS, MQ, KV, OM, SB, DA, and MN developed the data for the power analysis, completed the simulations, and/or associated statistical analysis plan. CS, JV, MM, AM, BZ, TG, DA, and MN contributed to the development of the substudies and data repository. CS, JV, OS, DA, and MN oversaw the digital embedding of the SPRY-Application. KR and JV were the major contributors in writing of the manuscript. All authors read and approved the final manuscript.

Data Statement Section

Technical appendix and simulations were completed by Berry Consultants, LLC and are available within appendix of this publication.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Tables

Table 1. Core Protocol and SPRY-Metformin Domain-Specific Appendix Inclusion and Exclusion Criteria

SPRY
Inclusion Criteria
Adult (≥ 18 years of age)
Evaluation at any preoperative elective clinic within the healthcare system
Planned surgical intervention ≥ 7 and <180 days following the preoperative encounter
Exclusion Criteria
Clinician deems inclusion may be potentially harmful
Emergent surgical procedure
Patient has participated in SPRY within the proceeding 90 days
SPRY-Metformin[a]
Inclusion Criteria
Men and post-menopausal women who are ≥ 60 years of age or are <60 years of age with a Charlson Comorbidity Index >2
Ability to swallow non-crushed pills
Exclusion Criteria
Pre-existing type I or II diabetes mellitus
Metformin use in the prior 6 months
Known allergy to metformin
Acute or chronic metabolic acidosis with or without coma
History of lactic acidosis
History of excessive alcohol intake
Severe hepatic dysfunction
Acute or chronic metabolic acidosis
Hemodialysis, end-stage renal disease, or estimated glomerular filtration rate <45 in the 30 days prior to or on the day of in-person screening

[a] Those in the motor study must be >65 years of age with their home address <20 miles of the central healthcare system academic hospital.

Abbreviations: SPRY: Strategies to Promote ResiliencY.

SPRY-Metformin Protocol

Table 2. Secondary Endpoints

Postoperative index hospital course
Incidence and total duration of postoperative intensive care unit admission
Index hospital length of stay
Hospital discharge location
Index hospitalization mortality rate
Within 30 days of the index operation
Surgical site infection[a]
Surgical Site occurence[b]
Organ failure free days[c]
Within 365 days of study drug exposure
Incidence of re-operation
Number of participants with deep vein thrombosis
Number of participants with pulmonary embolus
Mortality
Hospital readmission rates

[a] Surgical site infection defined by National Surgical Quality Improvement Program [35]
[b] Surgical site occurrence defined by Ventral Hernia Working Group [36]
[c] Organ failure defined as mechanical ventilation, hemodialysis, or vasopressor exposure

SPRY-Metformin Protocol

Table 3. Longitudinal Quality of Life and Frailty Timeline

Baseline[a]	**Postoperative Day 30**	**Postoperative Day 90**	
	Phone		In-Person (Motor Subgroup[b])
EQ-5D	EQ-5D	EQ-5D	EQ-5D
MoCA-BLIND		FAQ	FAQ
		MoCA-BLIND	NIH Toolbox Cognitive
		Haying Sentence Completion Test	2-Minute Walk Test
		Confusion Assessment Method	Grip Strength

[a] Baseline occurs within 7 days of randomization and prior to the surgical intervention.
[b] Omit the phone evaluation and undergo an in-person evaluation on postoperative day 90.

Abbreviations: (MoCA)-BLIND: Montreal Cognitive Assessment; FAQ: Functional Activities Questionnaire.

Figure Legends

Figure1. Concentric Consort Diagram – SPRY Core Protocol (Panel A) and Domain-Specific Appendix SPRY-Metformin Overlying the Core Protocol (Panel B)

Panel A: The Core Protocol creates a research platform or infrastructure within clinical care for all enrolled into any SPRY Domain-Specific Appendix. This infrastructure includes virtual screening, informed consent, and randomization at preoperative clinic, automated perioperative electronic health record monitoring, and a primary outcome of 90-day hospital free days. Patient privacy is maintained and protected by the embedded application functioning behind the institutional firewall.

Panel B: The SPRY-Metformin Domain-Specific Appendix functions within the infrastructure of the SPRY Core Protocol. Prior to preoperative clinic, the SPRY-Application screens the scheduled preoperative clinic appointments and generates a list of potential patients for enrolling clinicians. In preoperative clinic recruitment, informed consent, and randomization are completed. Patients undergo baseline testing. Study drug exposure begins and continues through postoperative day 90 (green). The SPRY-Application (light blue) supports patient safety monitoring by generating EHR and email alerts, as needed. As possible, all trial aspects are embedded within the standard of care perioperative course. When 500 patients surpass postoperative day 90, *a priori* interim analysis is completed. Future enrollment is then guided by the pre-determined response adaptive randomization schemes and predetermined stopping rules.

SPRY-Metformin Protocol

Abbreviations: REMAP: Randomized embedded multifactorial adaptive platform; SPRY: Strategies to Promote ResiliencY; POD: postoperative day; HIPAA: Health Insurance Portability and Accountability Act.

Figure 2. Virtual and In-Person Screening and Randomization

[a] <7 or >180 Preoperative Days

[b] Charlson Comorbidity Index (CCI) required within the 365 days prior to screening.

Virtual recruitment is completed by SPRY-Application (light blue) reviewing a subset of SPRY and SPRY-metformin enrollment criteria. The SPRY-Application then guides the clinical provider to complete the in-person screening and informed consent. Any discrepancies found between the clinical parameters within SPRY-Application and the patient's reported health state are manually updated within the EHR and patients are randomized.

Figure 3. SPRY-Metformin Timeline

[a] If patients are discharged on the day of the surgical intervention, lab sample 4 will be omitted. If hospital discharge occurs prior to postoperative day 3, lab sample 4 occur immediately prior to discharge

[b] Longitudinal testing at contact point 6 testing is dependent on participation in the motor subgroup (Table 3)

Patients are recruited, consented by providers, randomized, undergo baseline venous blood sampling, and are provided study drug at preoperative clinic (contact point 1). In the 7 to 180 preoperative days, patients undergo baseline testing (Table 3) and both patient safety and study drug compliance is monitored via phone interview (contact point 2). Three venous blood samples are coupled with clinical blood draws throughout the operative hospital admission

(contact point 3). A final venous sample is collected in standard of care postoperative clinic (contact point 4). At postoperative day 30 and 90, patients are contacted to monitor both patient safety and study drug compliance, collect postoperative outcomes (Table 2), and complete additional outcome testing (Table 3).

Abbreviations: Strategies to Promote ResiliencY, SPRY; Charlson Comorbidity Index, CCI; diabetes mellites type 1, DM1; diabetes mellites type 2, DM2; estimated glomerular filtration rate, eGFR; randomized embedded multifactorial adaptive platform, REMAP.

Figure 4. REMAP SPRY Administrative Organization

The Trial Steering Committee receives trial updates from the Statistical Monitoring Committee as well as recommendations from the Data and Safety Monitoring Board to oversee all trial conduct.

Abbreviations: Strategies to Promote ResiliencY, SPRY.

A

ADAPTIVE PLATFORM

Data Safety & Monitoring Board

INSTITUTIONAL FIREWALL

HIPAA Protected Patient Information

MULTIFACTORIAL TESTING

Virtual Screening & Recruitment

PREOPERATIVE CLINIC

Informed Consent

Randomization

Preoperative Clinical Planning

7-180 Days

ELECTIVE OPERATION

POSTOPERATIVE CLINIC

90 Day Hospital Free Days

POD 30

POD 90

Embedded Application

PERIOPERATIVE CLINICAL CARE

REMAP Core Protocol: SPRY

B

A PRIORI INTERIM ANALYSIS

Data Safety & Monitoring Board

INSTITUTIONAL FIREWALL

HIPAA Protected Patient Information

ADAPTIVE RESPONSE

STUDY DRUG EXPOSURE

Virtual Screening & Recruitment

PREOPERATIVE CLINIC

Informed Consent

Randomization

Preoperative Clinical Planning

Phone & Study Labs

Study Labs

Study Labs

Study Labs

Clinical Labs

Clinical Labs

ELECTIVE OPERATION

POSTOPERATIVE CLINIC

Phone

Phone

90 Day Hospital Free Days

POD 30

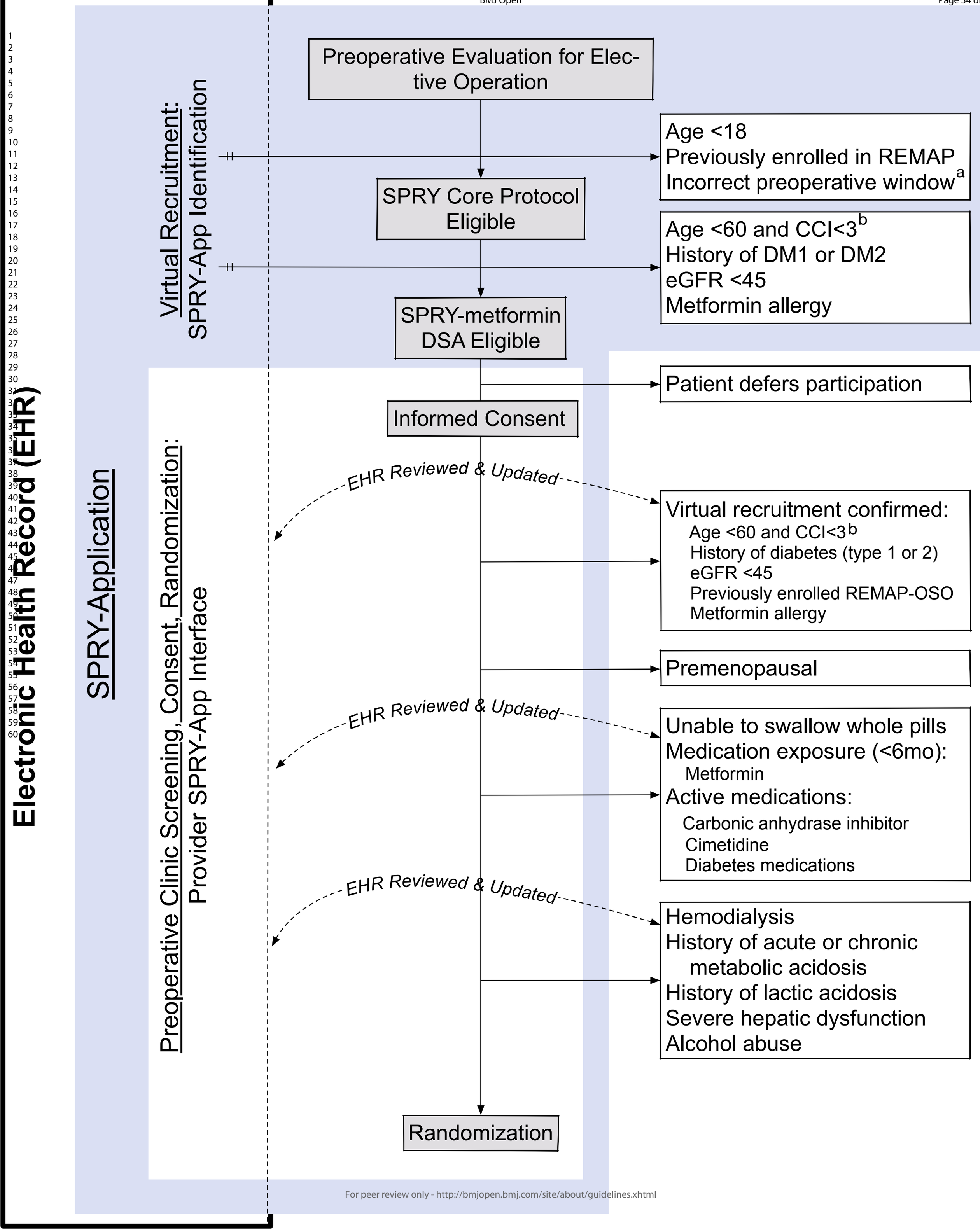
POD 90

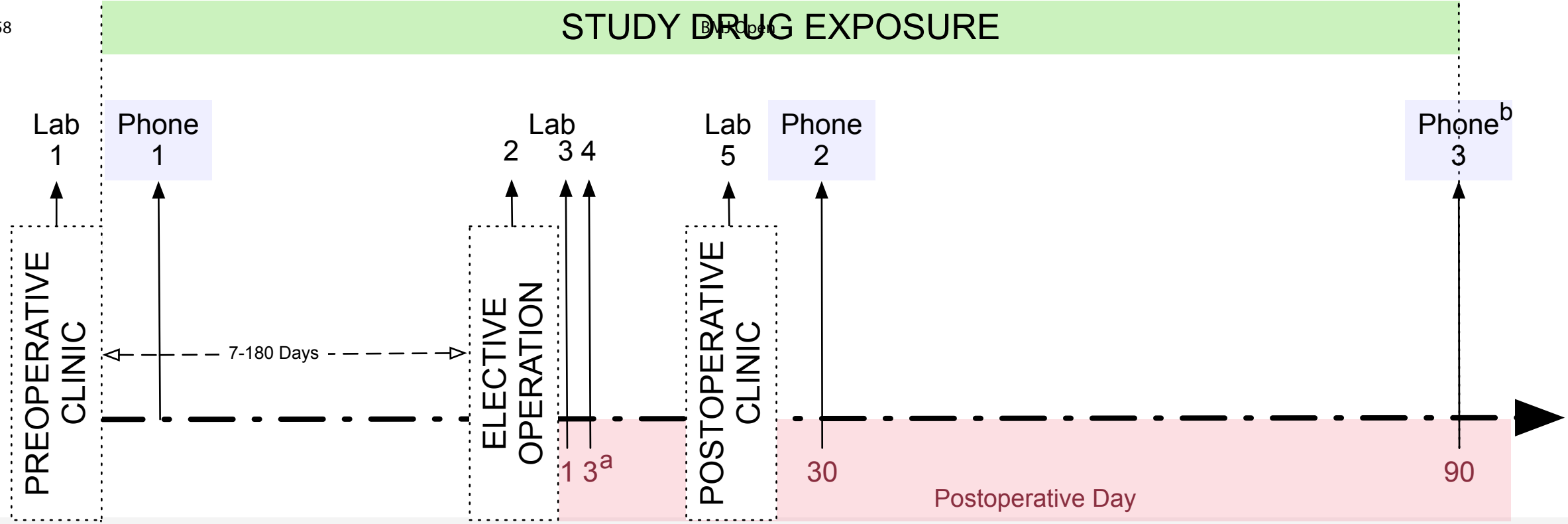
SPRY-App EHR Alerts

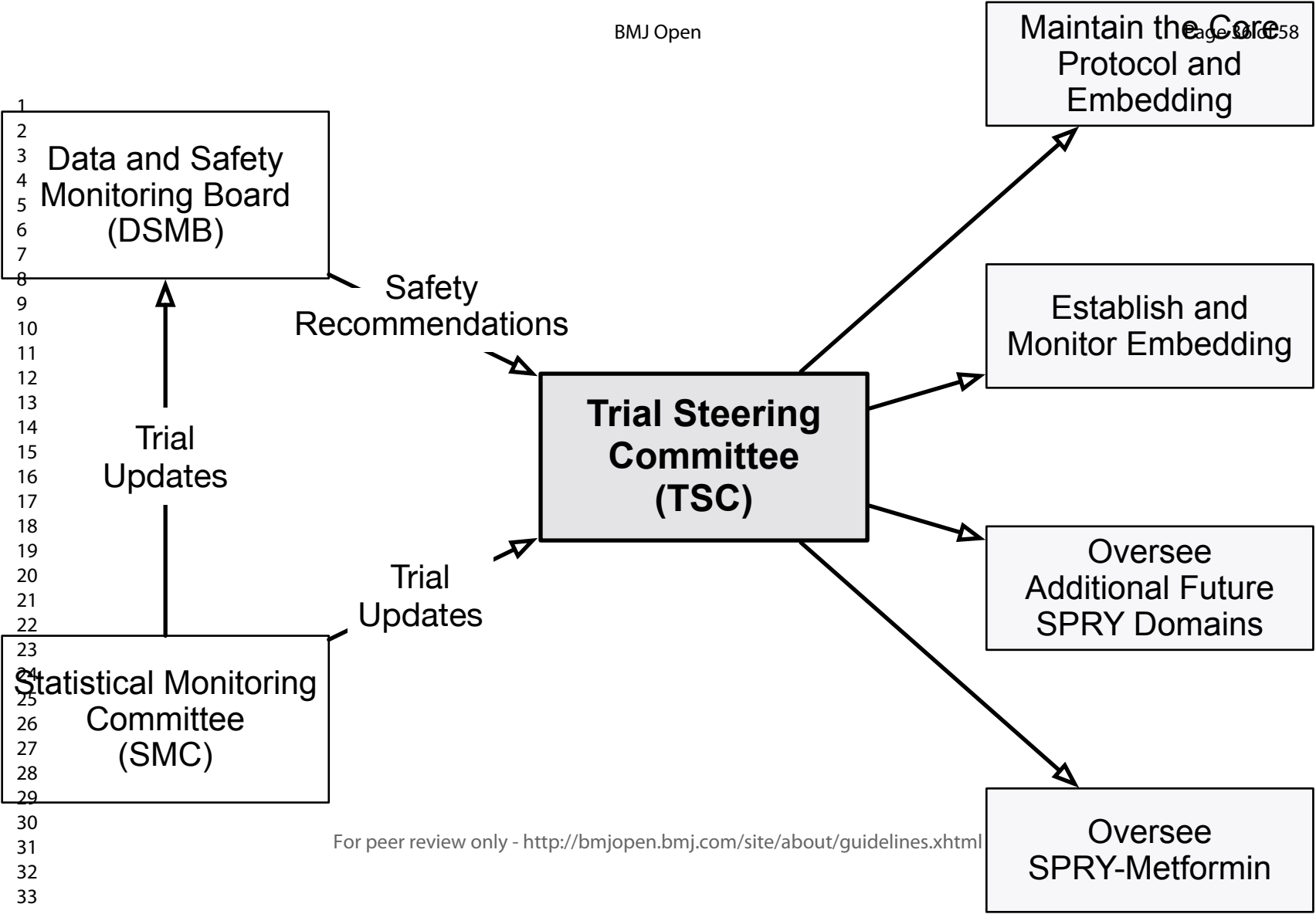
SPRY-Application

PERIOPERATIVE CLINICAL CARE

REMAP Domain-Specific Appendix: SPRY-Metformin







Adaptive Design Report for UPMC REMAP SPRY Randomized Controlled Trial of Metformin in High Risk Surgical Patients

1/1/20202

1.0 Introduction

SPRY is a randomized control trial comparing the effectiveness of different doses and durations of metformin to placebo for nondiabetic patients with elective surgeries. In particular, we will evaluate 3 doses of metformin (500, 1000 and 1500mg) as well as 3 levels of pre-op duration of metformin (short, 7-28 days; intermediate, 29-90 days; and long, 90 days). Patients will be randomized to one of the three metformin doses or placebo but will not be randomized to the pre-op duration. Pre-op duration will be observed based on the timing of the first pre-op visit.

The primary endpoint to determine efficacy of metformin relative to placebo is hospital free days (HFD) at day 90 after the surgical encounter after administration of metformin vs. placebo. HFD at day 90 is an ordered categorical variable that takes on discrete integer values from -1 to 90 and is calculated as 90 minus the number of days of the index stay and the number of days readmitted within the 90-day time period following the surgical encounter. If mortality occurs within the 90-day time period, the patient is given an HFD value of -1 (ordered to be a worse outcome than being in the hospital for all 90 days).

There will be a maximum of 2000-2500 patients randomized in the trial. Within each of the 3 pre-op durations, patients will initially be randomized $\sqrt{3}$:1:1:1 to placebo and the 3 doses of metformin until a total of 500 patients have been randomized across all pre-op durations and followed for 90 days. Afterwards, interim analyses will occur sequentially after an additional 500 patients have been followed for 90 days. At each interim analysis, the trial can be stopped early for demonstrating efficacy of one of the metformin doses compared to placebo (see Section 3.1). If the trial has not stopped for success and continues enrolling, within each pre-op duration doses can be dropped for futility and responsive adaptive randomization will be used to randomize patients preferentially to the best performing metformin doses of all of the remaining doses within that pre-op durations (see Sections 3.2-3.3). The trial can stop enrolling patients within a pre-op duration if all metformin doses have been stopped within that duration for futility (see Section 3.2). Finally, at the interim when 2000 patients have been randomized across all pre-op durations and followed for 90 days, the maximum sample size could be increased from 2000 to 2500 (see Section 3.4).

2.0 Statistical Modeling

Inferences and quantities of interest used for response adaptive randomization, success or futility of metformin doses, and increasing the maximum sample size in this trial are based a Bayesian ordinal logistic regression model that accounts for differences in the

expected 90-day HFD distribution depending on surgical procedure or strata of the patient.

2.1 Bayesian Ordinal Logistic Regression

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.

A Bayesian ordinal logistic regression model is used 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. 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:

$$Y_{c,i} \sim Bernoulli(\phi_{c,i}), c = 1 \dots 89;$$
$$logit(\phi_{c,i}) = \gamma_c + \mu_i;$$

where μ_i is a patient-specific mean function and γ_c is common across all patients.

The subject-specific mean function is as follows:

$$\mu_i = \alpha_{g(i)} + \theta_{t(i),d(i)}, i = 1 \dots N.$$

Within this model we assume that the underlying distribution of HFD is different within each stratum, *g*, and these differences across strata can be explained by a proportional log-odds ratio shift in the HFD distribution, α_g. 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 distribution $\theta_{t,d}$. Where a log-odds ratio $\theta_{t,d} < 0$ results in an increase in expected HFD. 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 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:

$$\theta_{t,d} = \beta_t + \kappa_d + \delta_{t,d} \quad for \; t > 1, t = 1 \dots 4, d = 1 \dots 3.$$

Here, β_t is the log-odds ratio due to the dose, κ_d is the log-odds ratio due to the duration and $\delta_{t,d}$ is an interaction between dose and duration.

2.2 Model Priors

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

$$\pi \sim Dirichlet(\alpha_{-1}, \cdots \alpha_{90});$$
$$\gamma_c = logit\left(\sum_{i=-1}^{c} \pi_i\right), c = 1 \ldots 89;$$

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

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

$$\alpha_g \sim N(0, 2^2), g = 1 \ldots G.$$

Within pre-trial data (discussed in Section 4), the standard deviation of the log-odds ratios across surgical types/strata was estimated to be 1.5.

We assume a hierarchical distributions for the dose-effects and duration-effects each centered around a common mean so there is borrowing of information across doses and durations:

$$\beta_t \sim N(\mu_\beta, .5^2);\ \mu_\beta \sim N(0,1), t = 1 \ldots 4;$$
$$\kappa_d \sim N(\mu_\kappa, .5^2);\ \mu_\kappa \sim N(0,1), d = 1 \ldots 3.$$

Finally, we assume that the interaction between dose and duration has a normal prior distribution with mean 0 and standard deviation .2 to limit the amount of deviation of the overall effect, $\theta_{t,d}$, from the two additive effects.

2.3 Quantities of Interest

The following statistical quantities are used in the design of the trial. The posterior distribution of all model parameters is calculated using MCMC. The algorithm allows the generating of M (ex. 100,000) draws from the joint posterior distribution for all model parameters.

2.3.1 Probability beat placebo by CSD

To determine if a dose should be dropped within a duration or if we should increase the sample size at N=2000, we summarize the posteriority probability that each dose and duration of metformin is superior to placebo by some clinically significant difference (CSD). The CSD is defined as an odds ratio of .8. Thus, we are interested in the

probability $\exp(\theta_{t,d}) < .8$. This quantity is calculated from the M samples of the posterior distribution of the effect of each dose and duration, $\theta_{t,d}$, by reporting the proportion of posterior samples in which the odds ratio, $\exp(\theta_{t,d})$ is less than .8:

$$\Pr\left(\exp(\theta_{t,d}) < .8 \mid Y\right) = \frac{1}{M}\sum_{m=1}^{M}\left(\exp(\theta_{t,d}) < .8\right), t = 1 \ldots 4, d = 1 \ldots 3.$$

2.3.2 Probability of Optimal Dose within each Duration

Within a pre-op duration, we will use response adaptive randomization to allocate the next set of patients to all doses that have not been stopped for futility based the posterior probability that each dose is optimal within each pre-op duration. This quantity is calculated from the M samples of the posterior distribution of the effect of each dose within each duration, $\theta_{t,d}$, by reporting the proportion of posterior samples in which the log odds ratio for dose *t*, $\theta_{t,d}$ is the min observed effect across all three metformin doses *t=2:4* with duration *d*:

$$O(t,d) = \frac{1}{M}\sum_{m=1}^{M} I[\theta_{t,d} < \theta_{j,d} \; for \; all \; j \neq t], t = 1 \ldots 4, d = 1 \ldots 3.$$

2.3.3 Probability of Superiority

To determine if the trial should stop early for success at any interim or if the trial is successful at the final analysis, we summarize the posteriority probability that each dose of metformin is superior to placebo. For the superiority analysis, we estimate the effect of each dose of metformin by pooling across all actively enrolling durations. This is achieved by using the model described in Section 2.1 with the additional assumption that $\theta_t = \theta_{t,1} = \theta_{t,2} = \theta_{t,3}$. The posterior distribution of the pooled effect of each dose, θ_t, is this estimated by calculating M samples of the posterior distribution using only data from the actively enrolling doses within each duration. The probability of superiority of each dose relative to placebo is then calculated as the proportion of the M samples with θ_t less than zero:

$$\Pr(\theta_t < 0 \mid Y) = \frac{1}{M}\sum_{m=1}^{M} \theta_t < 0, t = 1 \ldots 4.$$

3.0 Interim Analyses and Trial Adaptations

Before interim analyses begin, patients will be randomized √3:1:1:1 to placebo and the three doses of metformin within each pre-op duration. Interim analyses will then begin when 500 total patients across all doses and durations are randomized and have been followed for 90 days and will continue after every additional 500 patients have been followed for 90 days. Thus, there are 4 total interims at 500, 1000, 1500, and 2000

patients with 90-day follow-up and a final analysis when 2500 patients have been followed for 90 days. At each interim we allow the following adaptations:

- Success
- Dose / Duration Dropping
- Response Adaptive Randomization

3.1 Success

Success will be declared at an early interim or at the final analysis, and the trial will stop if the posterior probability of superiority of any dose of metformin relative to placebo defined in Section 2.3.3 is greater than a pre-defined interim-specific threshold. The thresholds for each interim are reported in Table 3.1.1 and are based on an O'brien Fleming spending function assuming a maximum sample size of 2500:

Table 3.1.1: Success Thresholds

Analysis	**500**	**1000**	**1500**	**2000**	**2500**
Success Threshold	***.9999***	***.9999***	***.9985***	***.9950***	***.9894***

3.2 Dose / Duration Dropping

Metformin doses will be dropped within a duration based on the probability of futility defined in Section 2.3.1. Specifically, for dose *t* in duration *d* if

$$\Pr\left(\exp\left(\theta_{t,d}\right) < .8 \mid \mathrm{Y}\right) < .15, t = 1 \ldots 4, d = 1 \ldots 3;$$

dose *t* will be dropped in duration *d* and patients within that duration will no longer be randomized to that dose.

We require an additional order restriction on dose dropping so that a dose must be dropped first in the short duration, then the intermediate duration then the long. Therefore, a dose cannot be dropped in the intermediate duration until it has first been dropped in the short and cannot be dropped in the long duration until it has first been dropped in the short and intermediate.

Enrollment to a pre-op duration will be stopped if all doses within that duration have been stopped and the trial will stop for futility if all pre-op durations have been stopped.

3.3 Response Adaptive Randomization within Durations

Within each pre-op duration of metformin, we will use response adaptive randomization to allocate patients to the most optimal dose of metformin within that pre-op duration. Initial randomization is set to $\sqrt{3}$:1:1:1 to placebo and the 3 doses of metformin within each duration. This allocates approximately .366 percent of the patients to placebo. This percentage allocation to placebo will be maintained throughout the course of the trial. However, after the first interim analysis, the remaining .634 percent of patients will be allocated to metformin doses within each duration that have not been dropped for futility and preferentially based on the probability that the dose is optimal within the duration defined in Section 2.3.2 and renormalized over the currently enrolling doses.

3.4 Increasing maximum sample size to 2500

At the interim analysis when 2000 patients are randomized and followed for 90 days the maximum sample size will increase to 2500 if at least one dose within one pre-op duration meets the following criteria:

$$\Pr\left(\exp\left(\theta_{t,d}\right) < .8 \mid \mathrm{Y}\right) > .50, t = 1 \ldots 4, d = 1 \ldots 3.$$

After 2000 patients have been randomized and are waiting to be followed for 90 days, enrollment will continue until the interim analysis takes place. If the above criteria is met, enrollment will continue to a maximum of 2500. If the above criteria is not met, enrollment will stop.

4.0 Clinical Trial Simulations

To create realistic clinical trial simulations, we obtained pre-trial data from patients within the UPMC electronic health records who had received an in-patient elective surgery and met the additional inclusion/exclusion criteria:

- Inclusion:
  - Age > 60 or RAI > 30 or CCI >2
  - Surgery performed in either PUH or SHY hospitals
- Exclusion:
  - Diabetes or previous metformin use
  - Had one of the following surgery types:
    - Minimally invasive cholecystectomy
    - Irrigation and debridement of a wound
    - Hyst. Total abdomen
    - Vaginal Hyst.
    - Sleeve Gast.

This resulted in data from 16,932 patients across 376 surgery types. Table 4.1 provides summaries of the data by clustering each surgery type into one of 14 surgical specialties. In particular, for each surgical specialty we report: total number of patients, total number of surgical types, mean and median HFD, and 90-day mortality rates.

Table 4.1: Summary Pre-Trial Data

	Total N	Surgical Procedures/ Strata	Mean HFD	Median HFD	Mort. Rate
Total	**16832**	**376**	**79.5**	**86.0**	**0.05**
ORTHO	3849	72	83.2	87.0	0.03
SPINE	2884	25	83.6	87.0	0.02
CARDIAC	1979	34	75.5	83.0	0.07
GENERAL	1692	52	70.9	82.0	0.10
UROLOGY	1221	21	85.2	88.0	0.01
THORACIC	1130	35	76.7	84.0	0.06
NEURO	1099	35	78.0	87.0	0.08
VASCULAR	1043	39	77.7	86.0	0.07
HPB	729	16	78.6	84.0	0.03
COLORECTAL	707	20	77.0	84.0	0.04
ENT	334	8	79.6	86.0	0.04
TRANSPLANT	136	8	71.0	81.5	0.01
GYNE	15	7	80.1	86.0	0.07
BARIATRIC	14	4	73.3	80.0	0.07

4.1 Virtual Patient Simulation

Within each simulation, we assumed that the SPRY trial would enroll subjects from all strata that had at least 50 subjects in the pre-trial data (77 total) with the proportion of patients within each enrolling stratum estimated from the pre-trial data. We also assume that the HFD distribution per strata under placebo is the same as what was observed in the pre-trial data. Finally, we assume treatment effects for each metformin dose can be summarized as a common percent reduction in the mean hospital days (HD) across all strata. This treatment effect is assumed to be 0% for all null scenarios and a maximum of 15% for all alternative scenarios. To obtain a common percent reduction in mean HD across all strata we find the strata-specific odds ratio shift under treatment relative to the empirical HFD distribution under placebo that results in the assumed common percent reduction in HD per strata.

For example, Figure 4.1 plots the assumed HFD distribution under placebo and under a 15% reduction in HD for the most common surgical type, Total knee arthroplasty. Within the pre-trial data there were 1115 patients who received a total knee arthroplasty. The empirical HFD distribution observed in the pre-trial patients and assumed for placebo within this stratum is plotted in blue with approximately 10% of patients having 89 HFD, 35% with 88 HFD and 29% with 87 HFD. Across all patients, the mean HFD is 86.6. To achieve a treatment effect of a 15% reduction in HD (plotted in green) we would need an odds ratio shift in the treatment distribution relative to placebo of .62. This would result in a mean reduction in HD of .5. This would shift approximately 15% of patients under treatment to 89 HFD, 42% to 88 HFD and 25% to 87 HFD.

Similar summaries for the 10 most common surgical types are provided in Table 4.2.

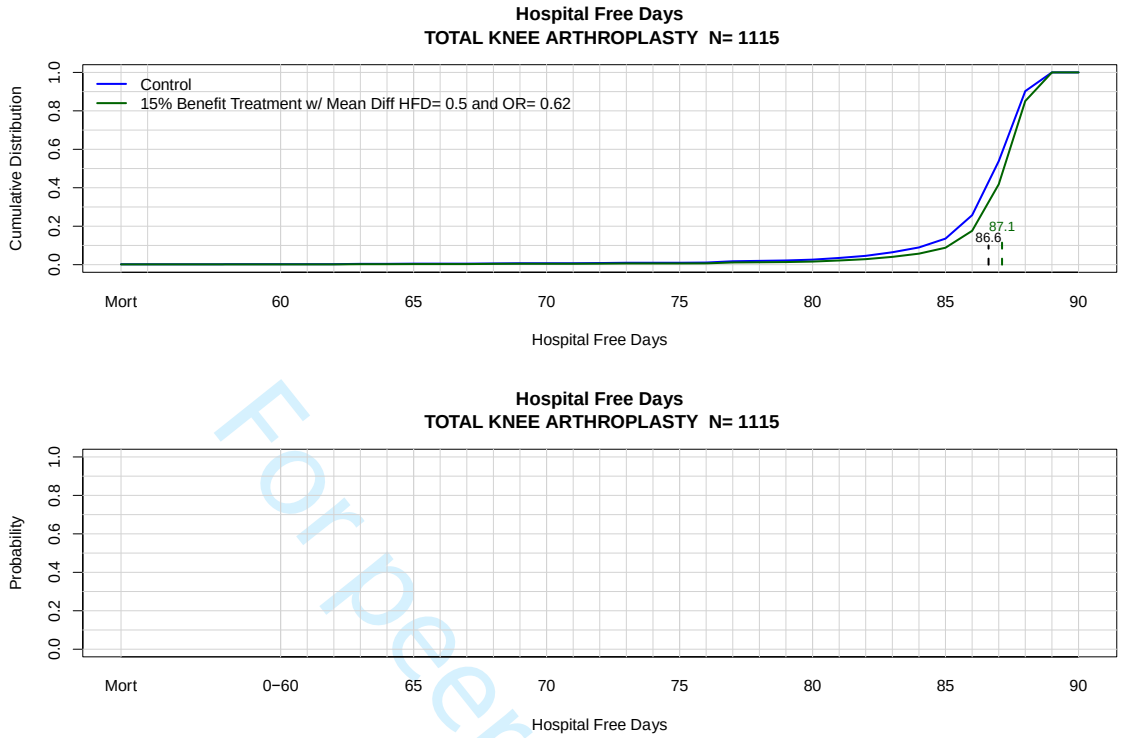


Figure 4.1: Example Strata-Specific HFD distribution under placebo vs. treated with a 15% reduction in HD for Total Knee Arthroplasty.

Table 4.2: Summary of Control Distributions and Treatment effects for 10 most common surgical types.

	Prop. Overall	Mean HFD Control	Mean Diff. Under Common 15% Reduction in HD	Odds-Ratio Shift Under Common 15% Reduction in HD
Total Knee Arth.	0.08	86.6	0.5	0.62
Spine Post. Fuse Internal Fix.	0.07	82.8	1.1	0.71
Total Hip Arth.	0.05	85.6	0.7	0.72
Endo. Aortic Valve Replace	0.03	79.2	1.6	0.78
Spine Ant. Cervical Dissect. and Fuse	0.03	86.2	0.6	0.77
Spine Post. Lumbar or Thoracic	0.03	84.7	0.8	0.77
MIS Partial Pulmonary Lobectomy	0.02	83.2	1.0	0.73
Prostatectomy Lap. Robotic Assist.	0.02	88.6	0.2	0.50
Laparotomy	0.02	64.1	3.9	0.76
Total Hip MIS 2 Incisions	0.02	88.0	0.2	0.76

5.0 Example Trials

We provide example data and results for two simulated example trials. In particular, for each interim in each example trial we provide a plot of the data and results (ex. Figure 5.1.1). Each plot shows the following:

- Top Left: Allocation to each dose and the number of patients within each duration for each dose.
- Top Middle: Mean estimates (circles) and CI for the ORs for each dose and duration of metformin as well as pooled for each dose (above the P and in grey) across all actively enrolling durations. The confidence intervals show the lower .15 quantile so that if the lower bar goes above .8 the dose may stop for futility and the upper Xth quantile where X is interim specific success threshold based on the success rules provided in Table 3.1.1 so that if the upper bar goes below 1 for the pooled estimate, the dose will be declared a success. Raw OR values are provided plotted as stars.
- Top Right: The new allocation probabilities within each duration for placebo and the 3 metformin doses.
- Bottom: Cumulative probabilities of observing each HFD value or less for Placebo and each dose of metformin averaged across all durations and separately within each duration. As the curves move down and to the right, the expected HFD is increasing and the number of expected HD is decreasing.

5.1 Example Trial 1

Figure 5.1.1 shows results from the first interim analysis when 500 patients have 90-day data. Approximately 200 patients have been allocated to placebo and 100 to each of the 3 metformin doses. Estimates for the OR of all doses (500, 1000 and 1500) given at the short duration are 1.2 or greater, all have a posterior probability that the OR < .8 less than 15%, and all are stopped for futility. Thus, the trial stops enrolling in the short duration. All doses are still enrolling in the medium and long durations. Within the intermediate duration the 1500mg dose has an OR estimated around .75, and the 1000 and 500mg have an OR estimated around .85. Therefore, the new allocation probabilities are weighted towards the 1500mg dose within the intermediate duration. Within the long duration the 1500 and 1000mg doses have an OR estimated around .6 and are preferentially allocated to over the 500mg dose which has an estimated OR of .85.

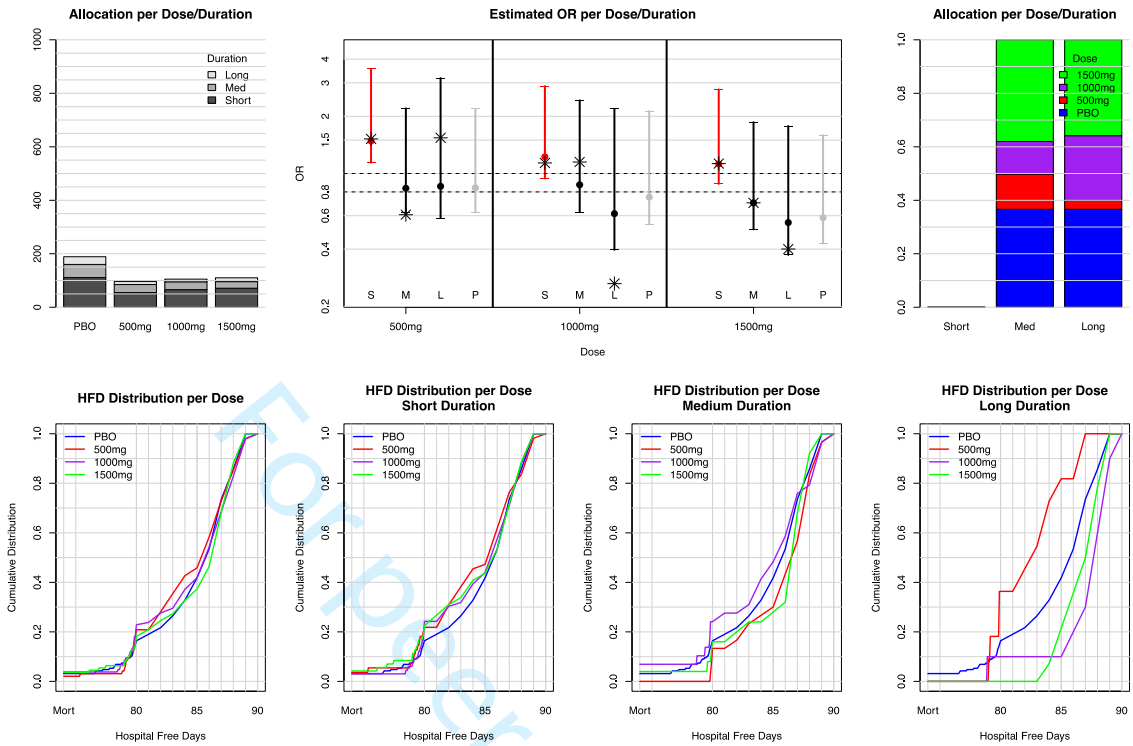


Figure 5.1.1: Example Trial 1; Interim N=500

Figure 5.1.2 shows results from the second interim analysis when 1000 patients have 90-day data. Approximately 375 patients have been allocated to placebo, 150 to 500mg, 200 to 1000mg and 300 to 1500mg. No new patients have been enrolled in the short duration. Within the intermediate duration the 1500mg dose has an OR estimated around .70, and the 1000 and 500mg have an OR estimated around .90. Therefore, the new allocation probabilities are weighted towards the 1500mg dose and away from the 1000 and 500mg dose within the intermediate duration. Within the long duration the 1500mg and 1000mg doses have an OR estimated around .65 and .75 respectively and are preferentially allocated to over the 500mg dose which has an estimated OR greater than 1. The 500mg dose in the long duration has less than a 15% posterior probability of having an OR < .8. However, it is not stopped since the intermediate duration has not stopped yet for this dose.

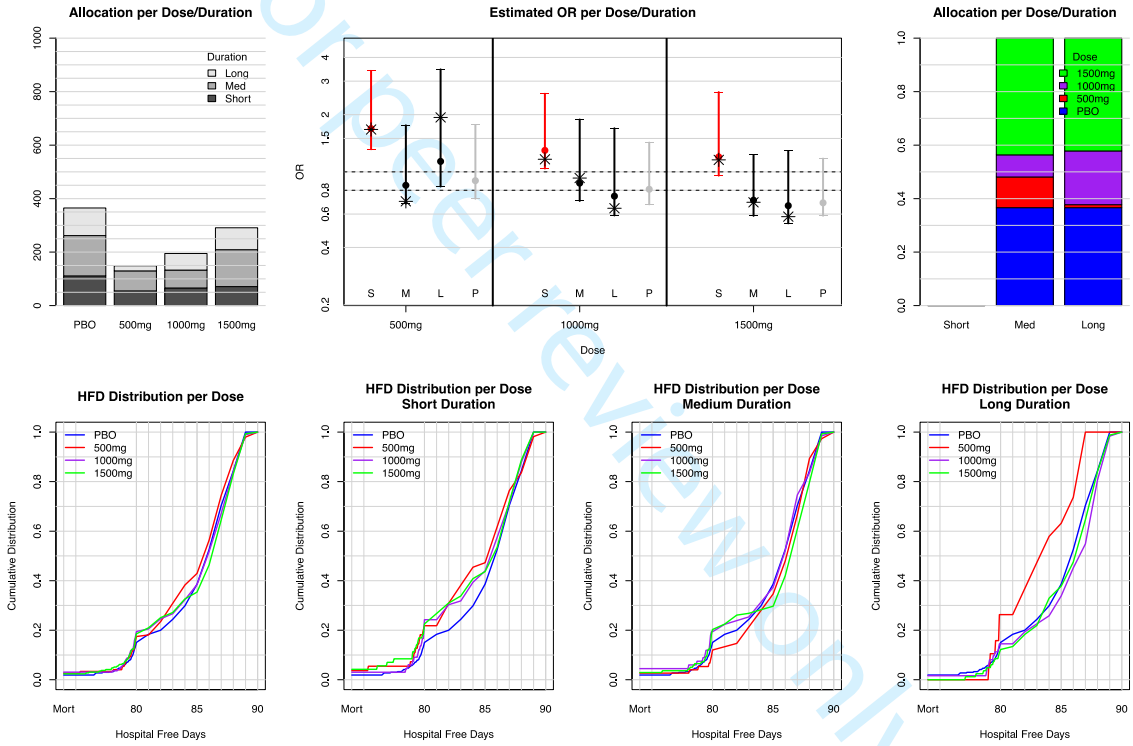


Figure 5.1.2: Example Trial 1; Interim N=1000

Figure 5.1.3 shows results from the third interim analysis when 1500 patients have 90-day data. Approximately 550 patients have been allocated to placebo, 200 to 500mg, 250 to 1000mg and 500 to 1500mg. No new patients have been enrolled in the short duration. The 500mg dose is stopped in both the intermediate and long durations. Within the intermediate and long durations, the 1500 and 1000mg doses have an OR estimated around .80 and have approximately equal allocations within each duration.

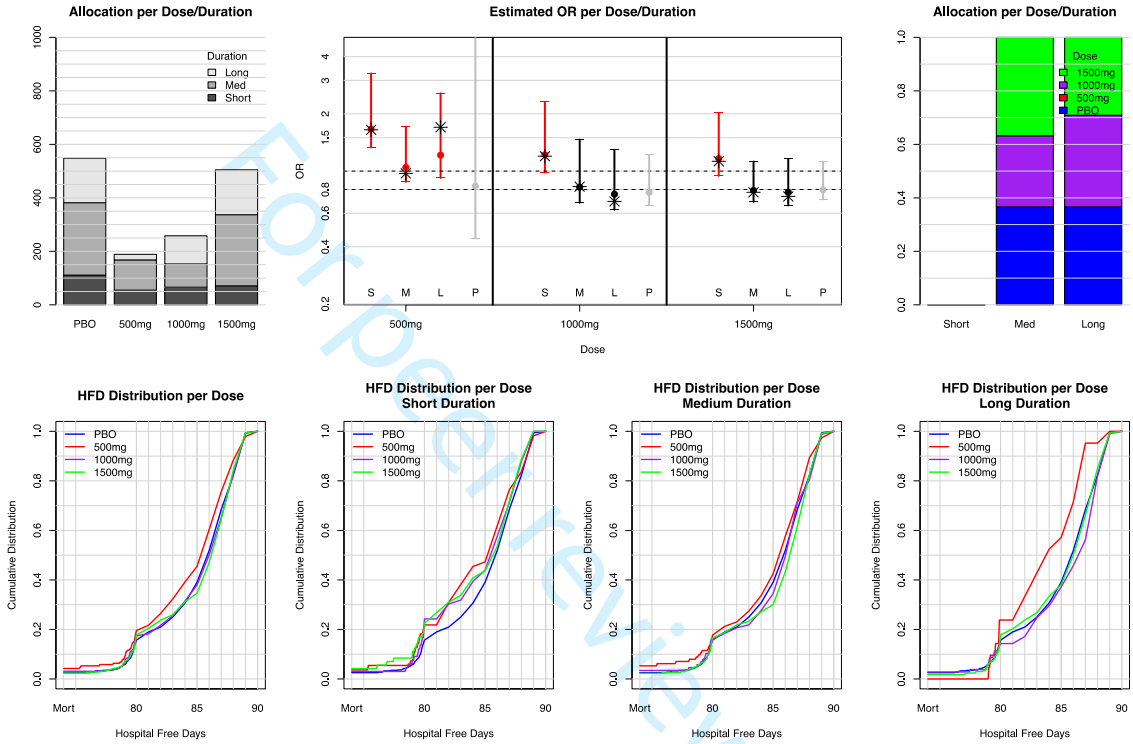


Figure 5.1.3: Example Trial 1; Interim N=1500

Figure 5.1.4 shows results from the fourth interim analysis when 2000 patients have 90-day data. Approximately 725 patients have been allocated to placebo, 200 to 500mg (no new patients), 425 to 1000mg and 675 to 1500mg. No new patients have been enrolled in the short duration. The pooled estimate across all actively enrolling durations (intermediate and long) for the 1000mg dose is approximately .75 and the upper limit of the CI has dropped below 1. Therefore, the posterior probability that the OR<1 for the 1000mg dose is greater than the interim-specific threshold (.995) and the study is stopped for success.

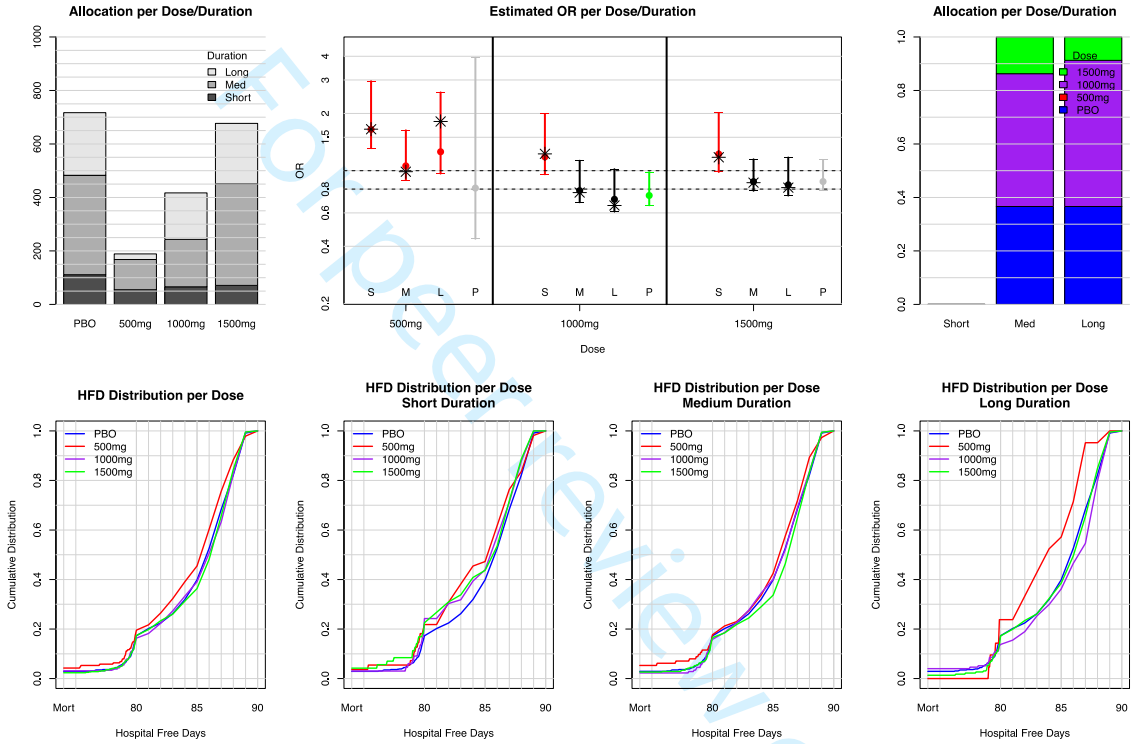


Figure 5.1.4: Example Trial 1; Interim N=2000

5.2 Example Trial 2

Figure 5.2.1 shows results from the first interim analysis when 500 patients have 90-day data. Approximately 200 patients have been allocated to placebo and 100 to 500, 1000 and 1500mg each. Within the cumulative distribution plots, the curves for each dose of metformin within each duration are mostly to the left and above the curve for placebo, indicating less HFD for each dose in each duration relative to placebo. For all doses within all durations the OR is estimated to be greater than 1.3 and the posterior probability that the OR < .8 is less than 15%. Thus, the trial stops for futility at the first interim analysis.

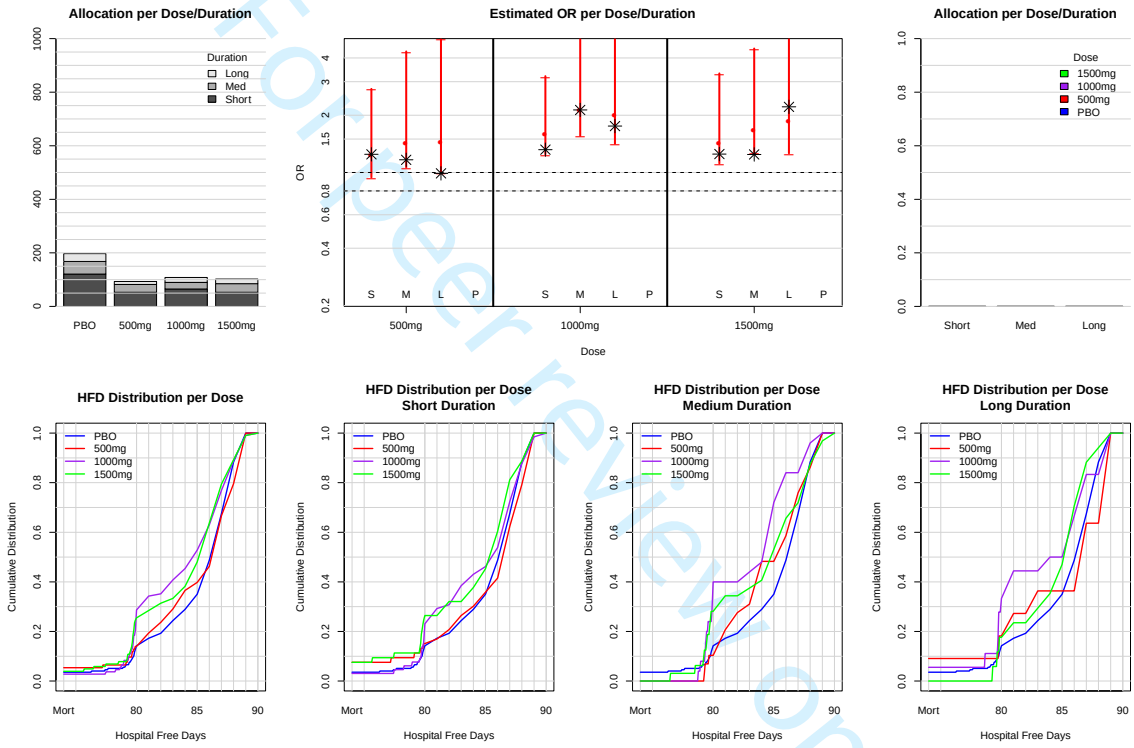


Figure 5.2.1: Example Trial 2; Interim N=500

6.0 Operating Characteristics

We simulate clinical trials under 7 possible treatment effect scenarios. Under the null scenario we assume that there is a 0% reduction in HD across all doses and all durations of metformin. Under all other scenarios we assume that the max effect is a 15% reduction in HD. The effect for each dose and duration is specified based on the dose-response and duration-response assumptions. We simulate under 3 different dose-response profiles. Under the "plateau" dose-response profile we assume a 7.5% reduction of the 500mg dose and a 15% reduction for the 1000 and 1500 mg doses. Under the "one good" profile we assume that there is a 0% reduction in HD for the 500 and 1000mg doses and a 15% reduction for the 1500mg dose. Under the "linear" profile, we assume a 3.75% reduction in HD for the 500mg dose, a 7.5% reduction for the 1000mg dose and a 15% reduction for the 1500mg dose. We also simulate under 2 different duration-response profiles, one where all durations work equally well and one where the intermediate and long durations work equally well but the short duration does not work for all doses. For each simulation we assume that 40% of the patients will have a short duration, 35% an intermediate duration and 25% a long duration.

Under each treatment effect scenario, we simulate 1000 clinical trials and report the following operating characteristics in Table 6.1:

- Probability of early success and total success
- Mean number of subjects enrolled in the trial
- Probability of stopping the short duration, intermediate duration or all of the durations
- Probability each dose is selected as best
- Probability increase sample size to 2500

The overall Type I error of the trial is 2.4% with 1% of the null trials stopping early for success and 91% of the null trials stopping early for futility or not increasing to the maximums sample size of 2500. The mean number of patients enrolled under the null scenario is 676. The probability the sample size is increased to 2500 under the null is 8%.

The power of the trial under the alternative scenarios ranges from 77-92% with the mean number of patients enrolled ranging from 1725 to 1822. When the short duration does not work, the probability of stopping the short duration is 80-84%. Across all alternative scenarios, we are choosing the right dose (a dose that has the maximum 15% reduction in HD effect) 79-96% of the time. Finally, the maximum sample size is increased from 2000-2500 21-31% of the time.

Table 6.1: Operating Characteristics											
Dose Response	Duration Response	Prob. Success		Mean N	Prob. Stop Futility			Prob. Selected Best			Prob. Enroll 2500
		Early	Total		Short	Int.	All	500	1000	1500	
Null	-	0.010	0.024	676	0.95	0.92	0.91	0.35	0.30	0.35	0.08
Plateau	All Work	0.75	0.92	1767	0.12	0.06	0.04	0.04	0.50	0.46	0.21
	Not Short	0.66	0.87	1822	0.86	0.15	0.09	0.06	0.44	0.49	0.26
One Good	All Work	0.67	0.86	1729	0.28	0.15	0.11	0.03	0.03	0.95	0.23
	Not Short	0.56	0.78	1725	0.83	0.28	0.19	0.06	0.04	0.90	0.26
Linear	All Work	0.64	0.84	1776	0.20	0.12	0.10	0.04	0.10	0.86	0.26
	Not Short	0.51	0.77	1782	0.82	0.24	0.17	0.07	0.14	0.79	0.31

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	15
Funding	#4	Sources and types of financial, material, and other support	23

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	23
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	23
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16-17
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants,			

interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10, 29
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-15, 16-17, 30
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	see figure 4
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including	15-16

		clinical and statistical assumptions supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9-12
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-11
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	17-18
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate	9-10

		measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-17, table 2
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17,18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these	2, 15, 18

		interim results and make the final decision to terminate the trial	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	2, 7
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16, 27-28
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17-18
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	14-15
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9-10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18, 24

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	15
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	14-15

Notes:

- 12: 13-15, 16-17, 30
- 13: see figure 4
- 20b: 15-17, table 2 This checklist was completed on 08. February 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Strategies to Promote ResiliencY (SPRY): A Randomized Embedded Multifactorial Adaptative Platform (REMAP) Clinical Trial Protocol to Study Interventions to Improve Recovery after Surgery in High Risk Patients

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Geriatric medicine, Evidence based practice, Surgery
Keywords:	Adult surgery < SURGERY, Clinical trials < THERAPEUTICS, SURGERY, Information management < BIOTECHNOLOGY & BIOINFORMATICS

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Strategies to Promote ResiliencY (SPRY): A Randomized Embedded Multifactorial Adaptative Platform (REMAP) Clinical Trial Protocol to Study Interventions to Improve Recovery after Surgery in High Risk Patients

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Word Count 3,365

Figures 4

Tables 3

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Abstract

Introduction: As the population ages, there is interest in strategies to promote resiliency, especially for frail patients at risk of its complications. The physiologic stress of surgery in high risk individuals has been proposed both as an important cause of accelerated age-related decline in health and as a model testing the effectiveness of strategies to improve resiliency to age-related health decline. We describe a randomized, embedded, multifactorial, adaptative platform (REMAP) trial to investigate multiple perioperative interventions, the first of which is metformin and selected for its anti-inflammatory and anti-aging properties beyond its traditional blood glucose control features.

Methods and analysis: Within a multi-hospital, single healthcare system, the Core Protocol for Strategies to Promote ResiliencY (SPRY) will be embedded within both the electronic health record (EHR) and healthcare culture generating a continuously self-learning healthcare system. Embedding reduces the administrative burden of a traditional trial while accessing and rapidly analyzing routine patientcare EHR data. SPRY-Metformin is a placebo-controlled trial, and the first SPRY domain evaluating the effectiveness of 3 metformin dosages across 3 preoperative durations within a heterogeneous set of major surgical procedures. The primary outcome is 90-day hospital free days. Bayesian posterior probabilities guide interim decision making with predefined rules to determine stopping for futility or superior dosing selection. Using response adaptative randomization, a maximum of 2,500 patients allows 77% to 92% power, detecting >15% primary outcome improvement. Secondary outcomes include mortality, readmission, and postoperative complications. A subset of patients will be selected for substudies evaluating the microbiome, cognition, postoperative delirium, and strength.

SPRY-Metformin Protocol

Ethics and dissemination: The Core Protocol of SPRY REMAP and associated SPRY-Metformin Domain-specific Appendix have been ethically approved by the Institutional Review Board and are publicly registered. Results will be publicly available to healthcare providers, patients, and trial participants following achieving predetermined platform conclusions.

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Strengths and Limitations

- The SPRY Core Protocol creates standardized trial elements shared multiple concurrent and sequential perioperative investigations, including SPRY-Metformin, preventing the continuous development and then dismantling of the expensive and complex clinical trial infrastructure.
- Digital trial embedding minimizes the work required by research staff to screen, randomize, and safely monitor patients within the perioperative period.
- The Bayesian analysis plan allows for borrowing of information on the treatment effect across multiple doses and durations of metformin to efficiency inform the research questions.
- Outcome data is automatically abstracted and supplemented by in-person inquiry, but may be limited or incomplete in patients who receive postoperative care within the multi-hospital healthcare system.
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Keywords

Randomized embedded multifactorial adaptive platform, REMAP, metformin, 90-day hospital free days, perioperative optimization, aging, prehabilitation

Introduction

By 2020, over 55 million Americans will be greater than 65 years of age [1]. The lifelong accumulation of stressors progressively leads to chronic disease and disability compromising homeostatic reserve. The complex interplay of cumulative medical, social, and functional generating these deficits, defined as frailty, are associated with but independent from age and leave individuals vulnerable to a physiologic insult further reducing resiliency [2,3]. In response, a broad range of multimodal therapies (e.g., smoking cessation, nutritional optimization, physical activity programs, etc.) are currently under investigation to both prevent and reduce the effects of aging on physiologic reserve [4]. However, as frailty is typically developed longitudinally, establishing treatment efficacy in clinical trials requires years to decades of outcome monitoring [5].

A lifetime of exposure to multiple, small stressors may cumulatively reduce reserve equal to that of few, severe stressors [6]. Elderly patients, at risk of frailty, undergo over one third of all surgical interventions and have an increased rate of postoperative morbidity and mortality for all levels of physiologic surgical stress [6–11]. According to the National Institute for Aging, the stress of a surgery is an “age-accelerating” cause of frailty [6], rapidly depleting resilience to secondary insults [12,13]. Therefore, a major surgical intervention is an efficient experimental model for evaluating novel strategies aimed at stabilizing, preventing, or reversing frailty [6].

Perioperative investigations strive to improve outcomes in an aged and at-risk population and also model loss of reserve or accelerated aging. We have therefore designed a randomized, embedded, multifactorial, adaptative platform (REMAP) [14] trial to evaluate the effectiveness of perioperative therapies within a multi-hospital single healthcare system: Strategies to Promote ResiliencY (SPRY). Metformin, the most commonly prescribed non-insulin medication for those with diabetes [15–17], has pleiotropic anti-inflammatory properties, and potentially slows the process of aging [18,19]. Therefore, we report the first of many trial

protocols evaluating perioperative therapies both concurrently and sequentially on this adaptive platform, SPRY-Metformin, randomizing patients to 3 dosages of metformin or placebo in parallel.

Methods and Analysis

Our protocol follows the SPIRIT guidelines which are individually addressed in **Appendix 1** [20]. The below content focuses on novel aspects of the SPRY Core Protocol and associated SPRY-Metformin Domain-specific Appendix.

Aims

The primary aim of SPRY is to establish the Core Protocol infrastructure for continuous and simultaneous adaptive analysis of multifactorial perioperative therapies (i.e., domains) evaluating their effect on resiliency to age-accelerating surgical stress in patients at risk for postoperative morbidity and mortality.

The primary aim of the SPRY-Metformin domain is to simultaneously establish the ideal duration and dose of perioperative metformin to determine its effectiveness as pharmacologic optimization across multiple surgical specialties.

Unified, the aims of the Core Protocol and all associated multifactorial Domain-specific Appendixes are to embed the study protocols both digitally within the electronic health record (EHR) and culturally among clinicians generating an efficient, cost-effective, patient centered and continuously self-learning healthcare system.

Trial Design

The design of the SPRY Core Protocol and associated Domain-Specific Appendices align with the recommendations of the Adaptive Platform Trials Coalition [21] and SPIRIT guidelines [20]. Specifically, SPRY will recurrently assess multiple, Trial Steering Committee (TSC) approved, domains in multiple surgical strata and disease subtypes using response adaptive randomization and a comprehensive statistical analysis plan to create a self-learning health system.

SPRY-Metformin Protocol

SPRY Core Protocol

SPRY is the first Core Protocol outlining the embedding of a trial within the EHR and routine perioperative healthcare delivery for at-risk, aged adults. The Core Protocol creates standardized trial elements shared by all applied domains, preventing the continuous development and then dismantling of the expensive and complex clinical trial infrastructure [22]. As with other adaptive platform trials, SPRY will assess multiple domains simultaneously using Bayesian statistical analysis and response adaptive randomization evaluating the treatment effect in predefined strata (e.g., vascular, orthopedic, hepatobiliary surgical interventions) [23,24]. In the REMAP design, patients can be randomized to one of many treatments within one of many simultaneously deployed domains resulting in multiple possible experimental treatment combinations. The Core Protocol allows for aggregation of the treatment response across different simultaneously investigated domains and the multifactorial evaluation of synergistic or antagonistic combinations within each of the strata.

SPRY trial flow per the Consolidation Standard of Reporting Trials (CONSORT) guidelines are adapted from the traditional linear format into a concentric diagram, demonstrating the perpetual nature of the Core Protocol (**Figure 1A**).

We provided details herein on the first SPRY Core Protocol Domain (SPRY-Metformin) (**Appendix 2**). Other, new domains will be added to the Core Protocol as emerging therapies become available. The TSC will consider the scientific validity of each domain, safety of concurrent therapies, and current enrollment rates when deciding to introduce a new domain concurrently or following existing domains. A new domain is introduced as a Domain-specific Appendix to the SPRY Core Protocol. This Domain-specific Appendix will be generated outlining potential interactions between multiple domains within the primary statistical analysis of efficacy, if deemed clinically appropriate. If multiple domains have been introduced, response adaptive

randomization will be based on best performing combinations of therapies within the multiple domains and incorporate potential interactions.

SPRY-Metformin Domain-Specific Appendix

SPRY-Metformin is a multi-hospital, single healthcare system, placebo-controlled, adaptive, phase 3 clinical trial that is blinded at the level of the patient, clinician, research team, and data analyst. SPRY-Metformin is the first domain to be launched on the SPRY Core Protocol testing the effectiveness of metformin in improving perioperative outcomes (**Figure 1B**). Patients are screened and recruited from preoperative clinic through a custom application communicating with EHR data (**Figure 2**). Study drug is started following randomization and continued throughout the perioperative period through postoperative day (POD) 90 (**Figure 3**). All patients are prospectively monitored through POD 365 with both automated EHR data collection and longitudinal patient follow up (**Appendix 3**).

Patient and Public Involvement

Patients were not invited to comment on the study design or result interpretation for the SPRY Core Protocol or SPRY-Metformin.

Trial Embedding

The integration of this trial into the EHR and clinical workflow requires two distinct forms of embedding: digital and cultural.

Digital Embedding

We developed Java-based (Oracle Corporation, Redwood Shores, CA) custom software, the SPRY-Application, which interfaces with the research team and EHR data. The digital embedding of the SPRY-Application serves multiple purposes. First, protecting the privacy of

trial patients. Second, automating patient screening, enrollment, and randomization while synchronizing research activities within perioperative standard of care clinical encounters. Third, accessing the robust EHR data generated as a part of routine patient care.

At UPMC, a two-factor authentication system safeguards all private patient information accessed through a single Citrix Workspace (Fort Lauderdale, FL) in accordance with Health Insurance Portability and Accountability Act. Like all protected data and programs within the healthcare system, the SPRY-Application resides behind this institutional firewall. Here, the SPRY-Application is distinct from, but communicates with EHR data. The SPRY-Application accesses the clinical research data repository within UPMC Clinical Analytics and is managed by Biostatistical and Data Management Core in the Department of Critical Care Medicine at UPMC. The data repository abstracts structured, raw data from the inpatient (CERNER Co., Kansas City, MO) and outpatient (Epic Systems Co., Madison, WI) EHR and generates accessible data tables. The data extraction process parallels the methodology used traditionally for retrospective EHR data collection and research [25–27]; however, these data are updated in real time.

Potential trial participant identification begins with the SPRY-Application screening. The SPRY-Application reviews SPRY specific, EHR data tables for each patient with a scheduled appointment at enrolling preoperative SPRY-Metformin clinics (**Figure 3**). The EHR of each scheduled patient is reviewed, generating a list of patients meeting a subset of inclusion and exclusion criteria. This list of potential SPRY-Metformin candidates is then automatically distributed to the study team and clinicians via institutional email for review.

In preoperative clinics, patients are offered the opportunity to participate in SPRY-Metformin. The SPRY-Application guides the clinician through the stepwise informed consent process (**Appendix 4**). Then, pertinent clinical biorepository EHR data auto-populates screening information within the SPRY-Application for review and confirmation with the patient (**Figure 4**). Any identified discrepancies between patient report and the EHR auto-populated SPRY-

Application data prompt the clinician to update the EHR (**Figure 1A**). This both minimizes trial data entry and maintains the accuracy of the EHR.

Patients meeting all inclusion and no exclusion criteria are allocated to a treatment regimen based upon the established randomization tables uploaded to the SPRY-Application. Automatically, the SPRY-Application then generates the study drug and laboratory prescription and synchronizes all research activities (e.g., blood and stool samples) within pertinent, scheduled perioperative standard of care clinical encounters. Throughout patient enrollment, the SPRY-Application monitors for biorepository updates to the Cerner Admission-Discharge-Transfer tables and informs the research team of hospital admissions and discharges for enrolled patients. Inevitable in-trial schedule changes can be manually updated within the SPRY-Application user interface and therefore adjusts the research activity timeline, updating research personnel, and distributing additional study drug, as needed, via the mail.

Cultural Embedding

SPRY-Metformin is designed with the intent to rely heavily on bedside clinicians for many aspects of trial execution. Healthcare system staff within high volume surgical clinics are busy with existing patient care responsibilities. We have attempted to minimize the burden of research in two ways. First, whenever possible, the protocol is fused within existing care activities. Second, we focus on engaging, educating, and motivating the entire clinical team.

For example, as each new site is identified, prior to site initiation, the research team informs the clinical team about the potential benefits of a REMAP trial design and a self-learning healthcare system. Simultaneously, the clinical team educates the research team on their patients' experiences and the clinic or unit specific workflow. Both teams generate clinic or unit specific protocols and SPRY-Application user manuals.

Study Population

The evaluation of enrollment criteria for the study population occurs across two formats and at two levels. Initially, a subset of criteria is screened in a digital format by the SPRY-Application. Subsequently, in face-to-face clinic format the consenting clinician confirms all inclusion and exclusion criteria. As prompted by the SPRY-Application, any discrepancies found between the data within the SPRY-Application and the patients' reported health state are manually updated within the SPRY-Application and EHR (**Figure 4**).

At the first level, patients exposed to the stress of an elective surgical intervention are identified. At the second level, participants are evaluated against the inclusion and exclusion criteria of the SPRY-Metformin domain identifying patients who, i) can be safely exposed to metformin and ii) are at risk of decreased physiologic reserve (i.e., older age and/or medical comorbidity) conferring postoperative morbidity and mortality at all levels of surgical stress (**Table 1**) [3,10]. Patients randomized in SPRY-Metformin can also participate in either or both substudies (microbiome or motor) as well as additional future domains on the SPRY Core Protocol.

SPRY-Metformin Intervention

Metformin Rationale

We hypothesize that pharmacologic perioperative optimization will improve surgical outcomes for an aged, frail patient population. Metformin, the most commonly prescribed non-insulin medication for type 2 diabetics, is one such therapy [15–17]. In multiple studies, metformin has an excellent safety profile, is well tolerated, and consistently delays the aging process and minimizes deleterious cellular inflammation [5] through effects on cellular respiration [28], muscle function [29], and the microbiome [30]. Metformin advantageously modulates the body's response to physical stress through its systemic anti-inflammatory properties [31,32] and appear to be independent of blood glucose control [32].

SPRY-Metformin Protocol

Study Drug

Both the duration and dose of study drug exposure will be evaluated. Patients are stratified based upon the anticipated perioperative duration: short (7-28 days), intermediate (29-90 days), or long (91-180 days). Within each duration window, patients are randomized to one of three doses of metformin extended release 500, 1000, or 1500mg, or placebo. Study drug is initiated the day following randomization and continued through postoperative day 90 without planned interruption perioperatively (**Figure 2**).

EHR Embedded Safety Alerts

Surgical stress can cause fluctuation in organ function perioperatively. As a part of routine clinical care, patients at the greatest risk of physiologic derailment and significant postoperative complications are admitted for postoperative monitoring. In real time, the SPRY-Application generates “pop-up” style inpatient EHR alerts prompting the bedside nurse to hold study drug administration in the setting of current (i.e., estimated glomerular filtration rate <45 or serum lactate ≥ 4) or potential future (i.e., ordered contrasted imaging studies) organ dysfunction (**Figure 2**). Simultaneously, the SPRY-Application generates an institutional email notifying the research team.

Endpoints

The primary endpoint of SPRY Core Protocol hospital free days (HFD) up to 90 days [33–36]. This composite endpoint is an ordered categorical variable defined as the number of days from the day of surgery to the 90 thereafter, during which the patient is alive and free of hospitalization and was chosen for three reasons. First, this composite variable quantifies the care required for patients with reduced physiologic reserve with an increased risk of both specific postoperative complications (i.e., wound infections) and overall progression of frailty

(i.e., progressive sarcopenia resulting in a fall and hip fracture) resulting in fewer HFD [10,37–41]. Second, HFD is weighted (i.e. -1) to address potential effects on mortality, independent of the cause and time of mortality within 90 days, throughout the 90-day postoperative period [33]. Third, time out of the hospital quantifies clinical outcomes and the cost of resource utilization, but reflects postoperative events important to patients and their families [42]. Therefore, HFD captures any treatment associated enhancements in resiliency across surgical strata and is applicable to SPRY-Metformin and any domain on the SPRY Core Protocol. The predefined and validated secondary clinical endpoints are listed in **Table 2** and **Table 3** [42–45].

Patient Sample Biorepository

An additional long-term goal of SPRY-Metformin is to understand the molecular mechanisms by which metformin might attenuate the inflammatory response and improve outcomes after surgical stress.

Statistical Analysis

The primary analysis plan for SPRY-Metformin includes a Bayesian ordinal logistic regression analysis of 90-day HFD to allow for borrowing of information on the treatment effect across different doses and durations of Metformin to maximally inform the research questions while minimizing the required patient sample size [46,47]. Complete documentation of the statistical analysis plan is including in the Statistical Analysis Appendix (**Appendix 2**).

Simulations and Sample Size Generation

Clinical trial simulations are used to optimize clinical trial design (best thresholds for early success, dose dropping, and futility stopping), to determine the sample size needed within this trial to obtain at least 80% power for a clinically meaningful treatment effect and a one-sided 2.5% type I error under the null distributions, and to quantify additional operating characteristics

of the SPRY-Metformin trial. Utilizing pertinent retrospective UPMC EHR data, virtual patient datasets were created based on the observed distributions of the primary endpoint, 90-day HFD, within each stratum. Clinical trial simulations randomized patients to study drug and numerous trials were virtually executed, including all interim analysis and randomization adaptations. For simulated patients randomized to placebo, we assumed the primary outcome to be distributed similar to the observed 90-day HFD distribution per surgical strata within the UPMC EHR data. For simulated patients randomized to metformin, the distributions of 90-day HFD within UPMC HER data per surgical strata were shifted towards higher values of 90-day HFD being more likely based on a common percent reduction in 90-day hosptial days (90- [90-day HFD]). For examples of how the distributions were shifted see **Appendix 2, Figure 4.1** and **Table 4.2**. The minimum clinically meaningful effect size was assumed to be a common percent decrease of 15% in 90-day mean hospital days for the highest treatment dose. This was chosen because it is sensitive to absolute differences in hospital days and treatments may have a larger absolute benefit for those procedures that are expected to result in more hospital days (**Appendix 2, Table 4.2**) [34].

Trial behavior, such as power and type I error were summarized as the proportion of simulated trials that were successful under the alternative and null scenarios respectively. Patients will therefore be adaptively randomized to placebo or three doses of metformin, for a maximum sample size of 2,500 patients enrolled. The trial has at least 84% power to detect a treatment effect of at least a 15% reduction in mean hospital days for a minimum of one of the doses under the assumption that the dose has an equally effective percent reduction in mean hospital days across all three preoperative metformin durations. If a dose is not effective for the short preoperative duration, the trial has at least 77% power to detect a treatment effect of at least a 15% reduction in mean hospital days for at least one of the doses. Under the assumption that no doses are effective there is an overall one-sided type I error of 2.5%.

SPRY-Metformin Protocol

The motor subgroup will enroll up to one third of SPRY-Metformin trial patients. The microbiome and muscle biopsy subgroups are exploratory pilot substudies with 1,000 and 200 patients to be enrolled.

Response Adaptative Randomization and Interim Analysis

Initially, SPRY-Metformin will randomize a maximum of 2,000 patients. Within each of the 3 preoperative durations, patients will initially be randomized $\sqrt{3}$:1:1:1 to placebo and the 3 doses of metformin. Interim analysis is completed each time 500 patients have been randomized across all preoperative durations and followed for 90 POD. At each interim analysis, the trial can be stopped early for demonstrating efficacy, response adaptive randomization will be adjusted to preferentially randomize patients to the best performing treatment group, or dose(s) can be dropped for futility.

Analysis Plan

The primary analysis method of 90-day HFD within SPRY-Metformin is a Bayesian ordinal logistic regression model that accounts for differences in the expected 90-day HFD distribution depending on surgical strata and allows for borrowing of information across pre-op durations and doses of Metformin [47]. Within this model, the effect of each dose of metformin for each preoperative duration relative to placebo is characterized as a constant log-OR shift in the 90-day HFD distribution. The primary intention to treat analysis will include those who have been randomized. All missing data will be imputed based upon the median observed 90-day HFD value for each treatment arm and preoperative duration. Sensitivity analysis will explore a per protocol analysis and alterative imputation strategies that do not make missing at random assumptions. Exploratory analyses will investigate the heterogeneity of treatment effects across key patient subgroups including, patient age and frailty as well as operative stress and surgical strata.

SPRY-Metformin Protocol

Superiority of a metformin dose to placebo within SPRY-Metformin is determined based on the posterior probability that the pooled log-OR effect of that dose across all enrolling preoperative durations relative to placebo is less than 0, indicating a shift in the 90-day HFD distribution towards more HFD under treatment compared to placebo. Success is declared at an interim or at the final analysis if the posterior probability of superiority for any dose of metformin is greater than the pre-defined interim-specific success threshold. The thresholds are based on an O'Brien Fleming spending function assuming a maximum sample size of 2,500 [48].

SPRY-Metformin secondary outcomes will be analyzed using regression models that account for expected differences in surgical strata of the patient.

Additional domains and additional interventions within domains will be added to the SPRY Core Protocol. Treatment effects and treatment-by-treatment interactions can be added for each additional perioperative therapy.

Ethics and Dissemination

Both the Core Protocol and SPRY-Metformin Domain-specific Appendix were independently approved at the University of Pittsburgh Institutional Review Board (IRB# 18060039, 18060038) without a required Investigational New Drug exemption from the Food and Drug Administration. Three independent groups were established to provide oversight for SPRY-Metformin: TSC, Statistical Monitoring Committee (SMC), and DSMB. The details of the relationship between and responsibilities of these committees are discussed in detail in the **Appendix 1** and summarized in **Figure 4.**

Platform conclusion

In SPRY, a platform conclusion describes when a statistical trigger has been reached and, following evaluation by the DSMB and in conjunction with the TSC, a decision is made to conclude a domain or intervention within a domain for superiority, equivalence, or futility. Under

all circumstances, a platform conclusion leads to implementation of the result within the REMAP and under almost all circumstances a platform conclusion leads immediately to Public Disclosure of the result by presentation and publication by the SPRY research team.

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Declarations

Author Statement

KR, CS, JV, OM, SE, JH, SB, DA, BZ, AN, OM, and MN participated in the creation of the study concept, protocol implementation, and outcome selection. JV, CS, MQ, KV, OM, SB, DA, and MN developed the data for the power analysis, completed the simulations, and/or associated statistical analysis plan. CS, JV, MM, AM, BZ, TG, MD, BM, DA, and MN contributed to the development of the substudies and data repository. CS, JV, OS, DA, JK, OM, and MN oversaw the digital embedding of the SPRY-Application. KR, MQ, and JV were the major contributors in writing of the manuscript. All authors read and approved the final manuscript.

Data Statement Section

Technical appendix and simulations were completed by Berry Consultants, LLC and are available within appendix of this publication.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgements

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Tables

Table 1. Core Protocol and SPRY-Metformin Domain-Specific Appendix Inclusion and Exclusion Criteria

SPRY
Inclusion Criteria
Adult (≥ 18 years of age)
Evaluation at any preoperative elective clinic within the healthcare system
Planned surgical intervention ≥ 7 and <180 days following the preoperative encounter
Exclusion Criteria
Clinician deems inclusion may be potentially harmful
Emergent surgical procedure
Patient has participated in SPRY within the proceeding 90 days
SPRY-Metformin[a]
Inclusion Criteria
Men and post-menopausal women who are ≥ 60 years of age or are <60 years of age with a Charlson Comorbidity Index >2
Ability to swallow non-crushed pills
Exclusion Criteria
Pre-existing type I or II diabetes mellitus
Metformin use in the prior 6 months
Known allergy to metformin
Acute or chronic metabolic acidosis with or without coma
History of lactic acidosis
History of excessive alcohol intake
Severe hepatic dysfunction
Acute or chronic metabolic acidosis
Hemodialysis, end-stage renal disease, or estimated glomerular filtration rate <45 in the 30 days prior to or on the day of in-person screening

[a] Those in the motor study must be >65 years of age with their home address <20 miles of the central healthcare system academic hospital.

Abbreviations: SPRY: Strategies to Promote ResiliencY.

SPRY-Metformin Protocol

Table 2. Secondary Endpoints

Postoperative index hospital course
Incidence and total duration of postoperative intensive care unit admission
Index hospital length of stay
Hospital discharge location
Index hospitalization mortality rate
Within 30 days of the index operation
Surgical site infection[a]
Surgical Site occurence[b]
Organ failure free days[c]
Within 365 days of study drug exposure
Incidence of re-operation
Number of participants with deep vein thrombosis
Number of participants with pulmonary embolus
Mortality
Hospital readmission rates

[a] Surgical site infection defined by National Surgical Quality Improvement Program [43]
[b] Surgical site occurrence defined by Ventral Hernia Working Group [44]
[c] Organ failure defined as mechanical ventilation, hemodialysis, or vasopressor exposure

Table 3. Longitudinal Quality of Life and Frailty Timeline

Baseline[a]	**Postoperative Day 30**	**Postoperative Day 90**	
	Phone		In-Person (Motor Subgroup[b])
EQ-5D	EQ-5D	EQ-5D	EQ-5D
MoCA-BLIND		FAQ	FAQ
		MoCA-BLIND	NIH Toolbox Cognitive
		Haying Sentence Completion Test	2-Minute Walk Test
		Confusion Assessment Method	Grip Strength

[a] Baseline occurs within 7 days of randomization and prior to the surgical intervention.
[b] Omit the phone evaluation and undergo an in-person evaluation on postoperative day 90.

Abbreviations: (MoCA)-BLIND: Montreal Cognitive Assessment; FAQ: Functional Activities Questionnaire.

Figure Legends

Figure1. Concentric Consort Diagram – SPRY Core Protocol (Panel A) and Domain-Specific Appendix SPRY-Metformin Overlying the Core Protocol (Panel B)

Panel A: The Core Protocol creates a research platform or infrastructure within clinical care for all enrolled into any SPRY Domain-Specific Appendix. This infrastructure includes virtual screening, informed consent, and randomization at preoperative clinic, automated perioperative electronic health record monitoring, and a primary outcome of 90-day hospital free days. Patient privacy is maintained and protected by the embedded application functioning behind the institutional firewall.

Panel B: The SPRY-Metformin Domain-Specific Appendix functions within the infrastructure of the SPRY Core Protocol. Prior to preoperative clinic, the SPRY-Application screens the scheduled preoperative clinic appointments and generates a list of potential patients for enrolling clinicians. In preoperative clinic recruitment, informed consent, and randomization are completed. Patients undergo baseline testing. Study drug exposure begins and continues through postoperative day 90 (green). The SPRY-Application (light blue) supports patient safety monitoring by generating EHR and email alerts, as needed. As possible, all trial aspects are embedded within the standard of care perioperative course. When 500 patients surpass postoperative day 90, *a priori* interim analysis is completed. Future enrollment is then guided by the pre-determined response adaptive randomization schemes and predetermined stopping rules.

SPRY-Metformin Protocol

Abbreviations: REMAP: Randomized embedded multifactorial adaptive platform; SPRY: Strategies to Promote ResiliencY; POD: postoperative day; HIPAA: Health Insurance Portability and Accountability Act.

Figure 2. Virtual and In-Person Screening and Randomization

[a] <7 or >180 Preoperative Days

[b] Charlson Comorbidity Index (CCI) required within the 365 days prior to screening.

Virtual recruitment is completed by SPRY-Application (light blue) reviewing a subset of SPRY and SPRY-metformin enrollment criteria. The SPRY-Application then guides the clinical provider to complete the in-person screening and informed consent. Any discrepancies found between the clinical parameters within SPRY-Application and the patient's reported health state are manually updated within the EHR and patients are randomized.

Figure 3. SPRY-Metformin Timeline

[a] If patients are discharged on the day of the surgical intervention, lab sample 4 will be omitted. If hospital discharge occurs prior to postoperative day 3, lab sample 4 occur immediately prior to discharge

[b] Longitudinal testing at contact point 6 testing is dependent on participation in the motor subgroup (Table 3)

Patients are recruited, consented by providers, randomized, undergo baseline venous blood sampling, and are provided study drug at preoperative clinic (contact point 1). In the 7 to 180 preoperative days, patients undergo baseline testing (Table 3) and both patient safety and study drug compliance is monitored via phone interview (contact point 2). Three venous blood samples are coupled with clinical blood draws throughout the operative hospital admission

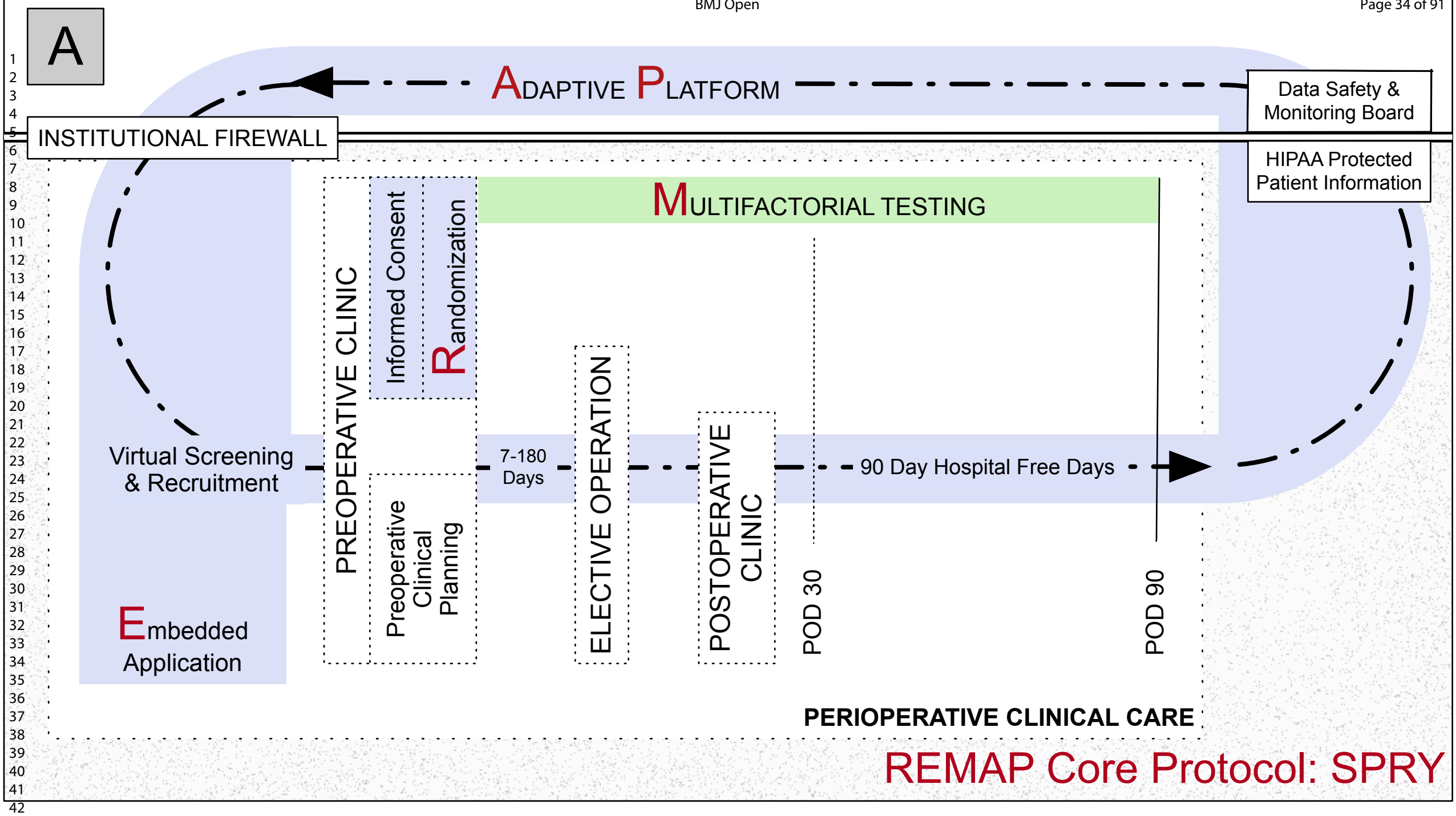
(contact point 3). A final venous sample is collected in standard of care postoperative clinic (contact point 4). At postoperative day 30 and 90, patients are contacted to monitor both patient safety and study drug compliance, collect postoperative outcomes (Table 2), and complete additional outcome testing (Table 3).

Abbreviations: Strategies to Promote ResiliencY, SPRY; Charlson Comorbidity Index, CCI; diabetes mellites type 1, DM1; diabetes mellites type 2, DM2; estimated glomerular filtration rate, eGFR; randomized embedded multifactorial adaptive platform, REMAP.

Figure 4. REMAP SPRY Administrative Organization

The Trial Steering Committee receives trial updates from the Statistical Monitoring Committee as well as recommendations from the Data and Safety Monitoring Board to oversee all trial conduct.

Abbreviations: Strategies to Promote ResiliencY, SPRY.



Electronic Health Record (EHR)

Virtual Recruitment: SPRY-App Identification

Preoperative Evaluation for Elective Operation

Age <18
Previously enrolled in REMAP
Incorrect preoperative window[a]

SPRY Core Protocol Eligible

Age <60 and CCI<3[b]
History of DM1 or DM2
eGFR <45
Metformin allergy

SPRY-metformin DSA Eligible

Patient defers participation

Informed Consent

SPRY-Application

Preoperative Clinic Screening, Consent, Randomization: Provider SPRY-App Interface

EHR Reviewed & Updated

Virtual recruitment confirmed:
- Age <60 and CCI<3[b]
- History of diabetes (type 1 or 2)
- eGFR <45
- Previously enrolled REMAP-OSO
- Metformin allergy

Premenopausal

EHR Reviewed & Updated

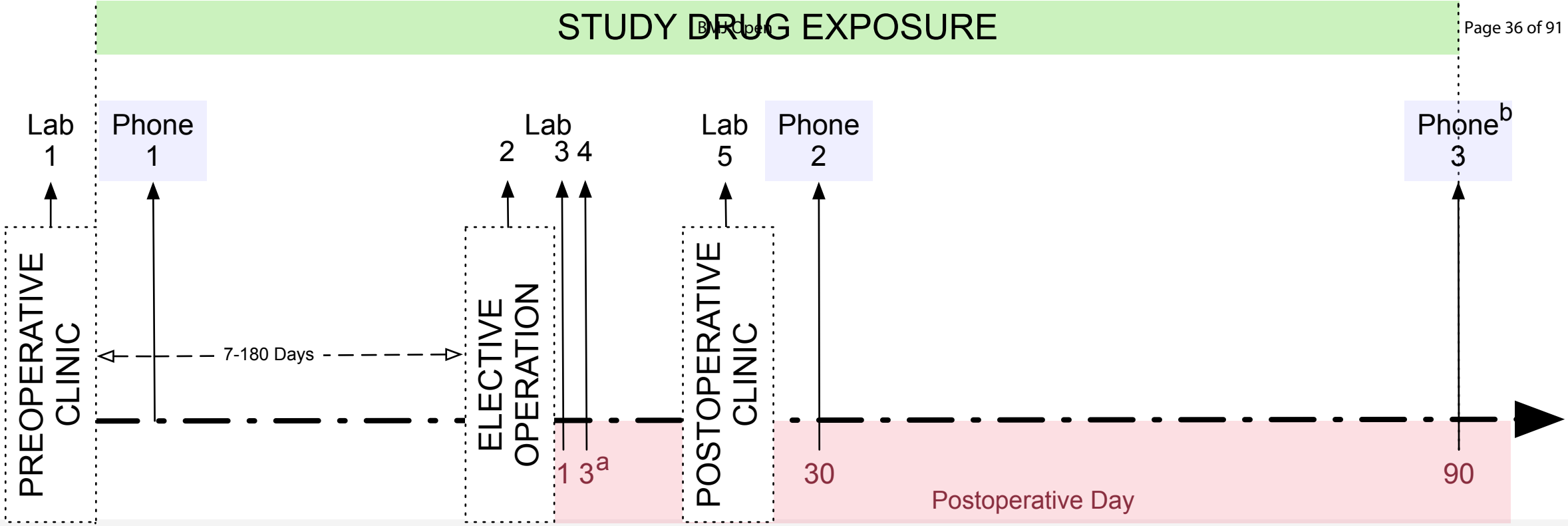
Unable to swallow whole pills
Medication exposure (<6mo):
- Metformin

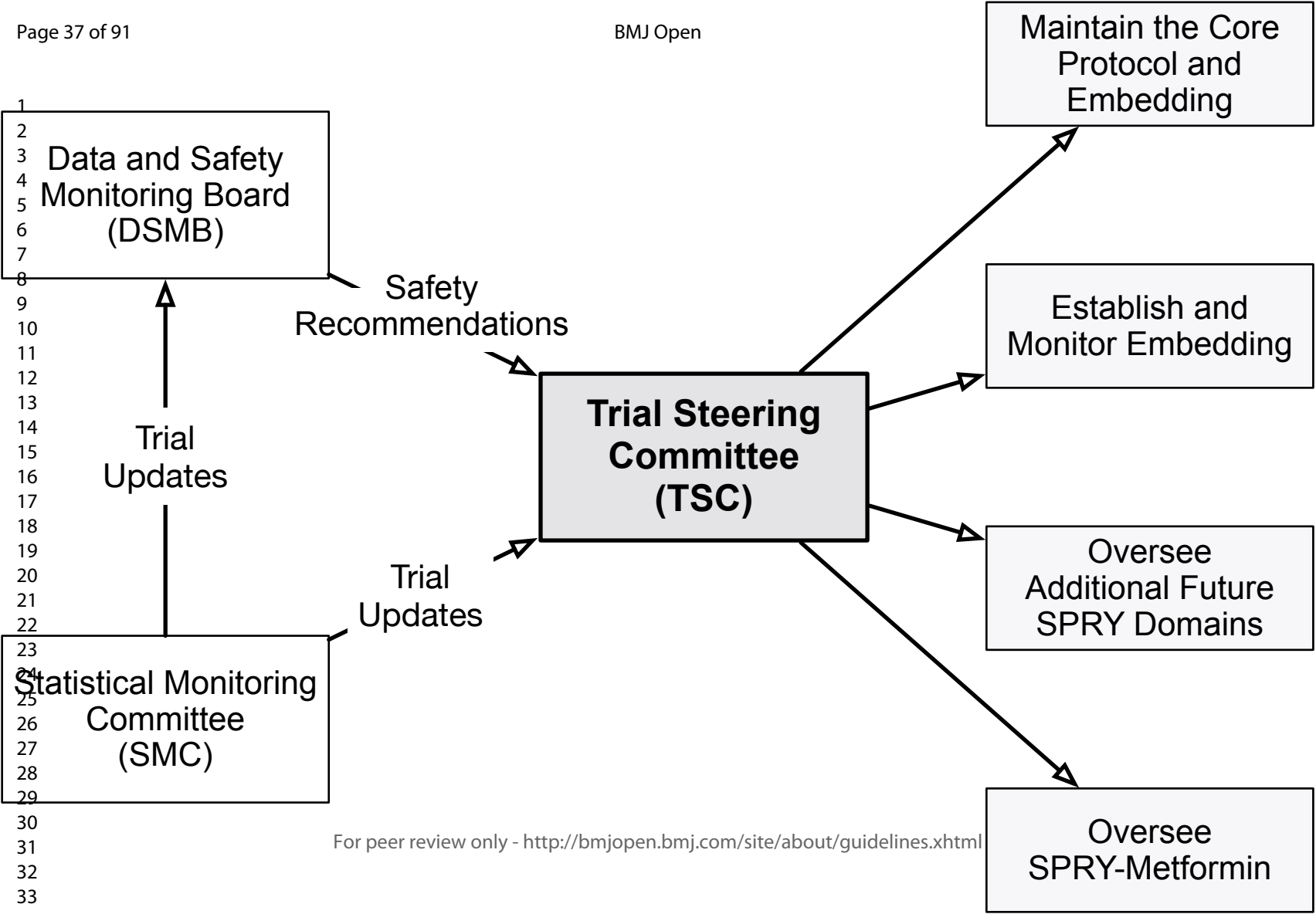
Active medications:
- Carbonic anhydrase inhibitor
- Cimetidine
- Diabetes medications

EHR Reviewed & Updated

Hemodialysis
History of acute or chronic metabolic acidosis
History of lactic acidosis
Severe hepatic dysfunction
Alcohol abuse

Randomization





SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **Strategies to Promote ResiliencY (SPRY): A Randomized Embedded Multifactorial Adaptative Platform (REMAP) Clinical Trial Protocol to Study Interventions to Improve Recovery after Surgery in High Risk Patients**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **Clinicaltrails.gov: NCT03861767**
	2b	All items from the World Health Organization Trial Registration Data Set **The most accurate and current information regarding the World Health Organization Trial Registration Data Set can be found on clinicaltrials.gov which is maintained by our research team, as mandated by our institutional review board.**
Protocol version	3	Date and version identifier **Please see ClinicalTrials.gov**
Funding	4	Sources and types of financial, material, and other support **This project is funded internally by UPMC through the UPMC Immune Transplant and Therapy Center.**
Roles and responsibilities	5a 5b	Names, affiliations, and roles of protocol contributors and Name and contact information for the trial sponsor **Protocol Contributors: KR, CS, JV, OM, SE, JH, SB, DA, and MN participated in the creation of the study concept, protocol implementation, and outcome selection. JV, CS, MQ, KV, OM, SB, DA, and MN developed the data for the power analysis, completed the simulations, and/or associated statistical analysis plan. CS, JV, MM, AM, BZ, TG, DA, and MN contributed to the development of the substudies and data repository. CS, JV, OS, DA, and MN oversaw the digital embedding of the SPRY-Application. KR and JV were the major contributors in writing of the manuscript. All authors read and approved the final manuscript. Please see the authorship list for the affiliation details.**

Trial Sponsor: UPMC Immune Transplant and Therapy Center

5c Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities

The UPMC Immune Transplant and Therapy Center are updated each quarter on the progress of this project. Study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication are decided by the REMAP SPRY and REMAP UPMC teams and are independent of The UPMC Immune Transplant and Therapy Center.

5d Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

Three independent groups were established to provide oversight for SPRY-Metformin: Trial Steering Committee (TSC), Statistical Monitoring Committee (SMC), and Data Safety and Monitoring Boards (DSMB). The blinded TSC oversees the overall trial conduct and makes recommendations regarding all trial-related decisions. The unblinded statisticians of the SMC are responsible for conducting and monitoring the interim analyses reporting patient enrollment, patient status, and a summary of trial adaptations based upon the pre-specified protocol. The DSMB, which constitutes expert clinical trialists, statisticians, and clinicians independent of the protocol contributors or trial sponsors. The DSMB reviews patient safety and protocol compliance reports generated by the SMC and makes trial conduct recommendations to the TSC (Figure 5).

Introduction

Background and rationale

6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

We hypothesize that pharmacologic perioperative optimization will improve surgical outcomes for an aged, frail patient population. The theorized mechanisms are discussed within the associated manuscript. Notably, however traditionally in diabetics, metformin is discontinued throughout the perioperative period because of both potential hypoglycemia and the theoretical risk of metabolic induced lactic acidosis. As monotherapy, metformin is not expected to cause hypoglycemia [1]**. Multiple cohort studies and meta-analysis have demonstrated the risk of metabolic acidosis to diabetics is not higher in those prescribed metformin** [2]**. Therefore, there is no expected risk of metformin induced lactic acidosis in those with adequate screening for renal and hepatic function** [2,3]**. Therefore, perioperative metformin is the first optimization strategy to be tested on the SPRY Core Protocol**.

6b Explanation for choice of comparators

		In the SPRY Metformin platform, three doses (500mg, 1000mg, 1500mg) of metformin will be compared to placebo. Although the literature supports salient inflammatory effects at lower doses[4,5]**, yet the dose required for a clinically meaningfully change in the primary outcome is unknown and the main objective of this platform. The posterior probabilities and pooled estimates, gleamed from a Bayesian statistical analysis plan and adaptive design which allows in trial assessment and adaptive randomization.** **We intend to use the placebo as an important control measure of not only clinical outcomes, but also for the exploratory data to be produced from samples provided within our biorepository. We have chosen to use randomization in conjunction with placebo in order to maintain allocation concealment and minimize systemic error including selection bias, performance bias, and ascertainment bias. Yet, our primary outcome cumulates objective outcomes (i.e., hospital length of stay, acute care hospital readmission, and death) into a single value – hospital free days. These measures are less likely to be altered by the patients, researcher's, or providers' perceptions of the therapy. Therefore, the objective outcomes and the desire to both maintain the pragmatic integration of the trial within the clinical standard culminated in the decision to minimize the in-trial assessment of compliance through only verbal confirmation during patient interactions.**
Objectives	7	Specific objectives or hypotheses **Please see the section, Methods/Design and subtitled Aims.**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Superiority trial with parallel group, adaptive randomization. Please see the Statistical Analysis Appendix.**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Recruitment, enrollment, consent, and study drug dose randomization occur within standard of care preoperative surgical and anesthesia clinic appointments at UPMC hospitals in southwestern Pennsylvania, USA.** **The study protocol is embedded within the workflow of both the electronic health record and the clinical care of patients. The final manuscript will include the list of enrolling clinics, the number of patients who were screened (both digitally and in-person) and enrolled per clinic, and the amount of clinical research staff support requested and required per clinic.**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

		Please see Table 1 for a full set of inclusion and exclusion criteria. Metformin prescriptions will be provided by medical doctors caring for and enrolling patients in preoperative clinics. Surgical interventions will be performed by attending surgeons at UPMC, as per the standard of patient care.
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Following confirming all inclusion and no exclusion criteria is met enrollment, and randomization study drug is provided to patients from established stock at each enrolling sight. Each study drug kit comes with the dosage specific number of 500mg of metformin ER or 500mg metformin ER matched placebo pills (i.e., two tablets per day for 1000mg metformin daily randomization). Patients allocated to the 1500mg arm are prescribed two 500mg tablets for seven days before ramping up to the full three tablet dose** [6]**. In the placebo arm, the same ramp up procedure and multiple dosages are used maintaining the blinded nature of this study**. **Study drug is maintained throughout the duration of the preoperative period into the postoperative period and for 90 days thereafter. Notably, the medication is not discontinued or held, unless deemed medically necessary by the research or clinical team, in the perioperative period.**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **Please see the section, EHR Embedded Safety Alerts.**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **Study drug compliance and patient safety are monitored prospectively via phone interviews completed throughout the study. To maintain the integration within clinical care, supported by cultural and digital embedding, study drug is not collected nor are systemic metformin levels assessed throughout the trial.**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **All standard of care perioperative care and interventions, as deemed appropriate by the clinical team are permitted.**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Please see the section, Endpoints within the manuscript; the following sections within the Statistical Analysis Appendix, 2.0 and 2.3; and SPIRIT guideline 18.**

Please note, potential and/or actual patients were not engaged when considering the current protocol or endpoints.

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **This trial has no run in or wash out periods. All patient interactions and the duration of active patient observation are seen and described within Figure 1, 2, and 4.**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **Please see Statistical Analysis Appendix, Section 3 and 4.**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **The simulations used to power this trial were generated from retrospective UPMC data. Therefore, the surgical volume and patients expected to meet all inclusion and no exclusion criteria is known and therefore is not expected to be a limitation of this study.** **The cultural embedding and generation of a self-learning health system is fundamental to the adequately enrolling patients. If trial enrollment is not on target at any or all sites, we will regularly meet with clinical and research staff within each clinic site. We will assess any issues with workflow, patient enrollment, and patient interest. Adjustments may then be made on a clinic level or for the entirety of the trial. Please see guideline 9.**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **Randomization is performed based on pre-specified randomization tables that utilize block randomization within each strata. Randomization is stratified by enrollment site, patient age, and the preoperative duration of study drug exposure.**
Concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **The Investigational Drug Service maintains an up to date log of study drug package available in each outpatient enrolling clinic. When the patient is randomized, the SPRY-Application then informs the clinical research team and/or clinical provider administering study drug which study drug packer, within that physical clinic, to provide the patient. Therefore, the SPRY-Application in conjunction with the Investigational**

			Drug Services are integral to allocating study drug and ensuring that patients, providers, the TSC, and clinical research staff are blinded.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**The allocation sequence is generated by the statisticians at the start of the trial and adjusted at each adaptive randomization time point. Patients are enrolled by either clinical research staff or clinical providers who are completing the standard of care patient encounter. The enrollment protocol is determined by the workflow within each clinic when the site begins enrolling patients and should be an iterative process to support the overall aim of generating a self-learning health system. In order to understand the effects of the clinical embedding on the trial results, clinic specific enrollment reporting is discussed in guideline 9.**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**Patients are randomly allocated to 1-3 tablets of daily metformin ER or 1-3 tables of daily placebo which matches metformin ER, with minor differences as required by the Food and Drug Association. Patients or providers may know that they are receiving either 500mg of metformin or 1 tablet of placebo. Therefore, trial participants, clinical care providers, research staff, and data analysts are all blinded to the allocation of metformin or placebo, but not to the potential dose of the study drug.**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**Unblinding is permissible if required by the TSC, SMC, or DSMB in order to maintain participant safety.**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**The primary outcome is 90-day hospital free days. If a patient is discharged and readmitted, then this hospital exposure is added to the duration of the primary admission. Hospitalizations within the healthcare system are monitored and recorded by the EHR embedded SPRY-Application. Out of system hospitalizations are reviewed at each postoperative point of contact (2, 5, 6; Figure 4). Emergency department and unplanned outpatient evaluations without admissions are not included in this composite. Any person who dies within this 90-day period is assigned -1 HFD, even if there is a period during which the patient is not within the hospital. Thus, mortality is**

			specifically captured, and this endpoint reflects the recovery for high-risk patients following a major surgical intervention. **Patient vitality, date and cause of death, is monitored in three ways in the clinical research data repository: 1) Prospective patient interaction at established contact points, 2) updates of electronic health record documentation of death within a UPMC healthcare system-based facility (e.g. nursing or rehabilitation facilities, emergency departments, and/or acute care hospitals), 3) monthly updates of the Social Security Administrative Death data files. Notably, when compared to a prospective patient registry, our combined (2) EHR vitality status and (3) Social Security Administrative data file is 94% sensitivity and 92% specificity. Therefore, in combination with prospective patient monitoring the internal validity of postoperative mortality is accurate.** **The predefined secondary endpoints include clinically significant and patient centered outcomes which have accepted, published, and validated definitions (Table 2). Further, the longitudinal quality of life and frailty outcomes (Table 3), are administered in accordance with test-specific, standard protocols by trained clinical research staff with experience with other prospective quantitative and qualitative patient assessments.** **Clinical research forms provided as an appendix.**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**The primary analysis follows an intention to treat analysis plan. Please see the statistical analysis plan and associated appendix for treatment of missing data.**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**Data quality is monitored on several levels. First, data is abstracted in real time form structured EHR data via tables generated commercially by CERNER and EPIC. Second, these data are monitored by UPMC Clinical Analytics in conjunction with Biostatistical and Data Management Core who provide oversight of these and other data abstract for the quality improvement of the healthcare system and research specific data. Data abstracted specifically for SPRY was collected retrospectively from a subset of non-study patients and validated against clinical adjudication. Third, data are monitored by the blinded TSC for face validity. Fourth, data collected by clinical research staff from patient encounters is recorded on the clinical research forms and uploaded into the data repository with value ranges appropriate for each variable.** **All EHR data is stored within the Biostatistics and Data Management Core at the CRISMA Center in the Department of Critical Care Medicine at the University of Pittsburgh.**

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **Please see the section, Statistical Analysis and the Statistical Analysis Appendix.**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **Please see the section, Statistical Analysis and the Statistical Analysis Appendix.**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		**Please see the section, Statistical Analysis and the Statistical Analysis Appendix.**
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **In this trial, data are managed by the Statistical Monitoring Committee (SMC), who are unblinded University of Pittsburgh Statisticians. This group works in conjunction with the TSC and DSMB to ensure the safety of those enrolled in our trial. The SMC has no competing interests to disclose. Notably, the interim and final data analysis for trial decision making including adaptive randomization and effectiveness will be completed by Berry Consultants, LLC, as discussed elsewhere.**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **Interim analysis is completed each time 500 patients have been randomized across all preoperative durations and followed for 90 postoperative days. At each interim analysis, the trial can be stopped early for demonstrating efficacy on any one of the metformin doses compared to placebo. If the trial has not stopped for success, the response adaptative randomization will preferentially randomize to the best performing metformin doses within each preoperative duration while maintaining the allocation to placebo. If there is a low posterior probability of efficacy (odds ratio, OR≤0.8), single or multiple doses can be dropped for futility. If all doses have been dropped within a preoperative duration, enrollment to that preoperative duration will be stopped. Finally, the maximum sample size will be increased from 2,000 to 2,500 if at least one dose within one preoperative duration has ≥50% posterior probability of efficacy (OR≤0.8).**

		The interim analyses and all resulting actions including updates to randomization probabilities are pre-specified and not subject to recommendations from the Data Safety and Monitoring Boards (DSMB). However, the DSMB may make recommendations regarding safety, trial conduct, or ongoing scientific validity, integrity, and both clinical and scientific relevance of the study. **Please see the section, Platform conclusion; and the Statistical Analysis Appendix.**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **Generally, only serious adverse events (SAE) that are not trial endpoints require reporting. SAE reporting is completed as a hybrid approach, with both automated monitoring and a more traditional patient interaction. Safety monitoring and EHR and email alerts, as discussed in the main protocol manuscript, include organ dysfunction (i.e., creatinine elevations and hepatic function abnormalities) and hospital admission/discharge notifications. These automated SAEs are supplemented by periodic chart review, completed by the research team, as well as patient interactions at key patient contact points throughout the postoperative monitoring period. At this time, patient wellness is confirmed, study drug compliance is discussed, and any the occurrence of any SAEs are addressed.** **All SAE data will be uploaded, with all other trial data, to the Biostatistical and Data Management Core.**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **For SPRY-Metformin, we have established a separate data and safety monitoring board (DSMB). The DSMB is comprised of individuals with expertise in adaptive clinical trials, statistics, aging, and perioperative care. Under a separate charter agreement, the DSMB will form and will, with autonomy, provide oversite and monitoring for this clinical trial. This monitoring includes, but is not limited to, clinical trial recruitment/retention processes, data timeliness and quality, and subject privacy and data confidentially aspect. This DSMB will review interim data analyses and will make recommendations on whether the study should continue, continue with modification, or terminate based upon these analyses. When the trial is actively enrolling patients, the DSMB will meet quarterly.**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Both the Core Protocol and SPRY-Metformin Domain-specific Appendix were independently approved at the University of Pittsburgh Institutional Review Board (IRB# 18060039, 18060038) without a**

		required Investigational New Drug exemption from the Food and Drug Administration.
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **Any and all protocol modifications will be reviewed by the TSC. If deemed necessary, appropriate updates to the IRB will be submitted for review. Once approved, any and all additional updates will be made to the trial registry (ClinicalTrials.gov), investigators, SMC and DSMB. If protocol adjustments require changes to the informed consent documentation, the IRB will help guide the TSC for patient notification and/or additional required consent for those actively enrolled.**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **SPRY-Metformin randomizes patients to study drug. Therefore, as mandated by our institutional review board, informed consent will be obtained by a physician or provider with a license to prescribe medications to patients.** **Please see the sample patient consent form (Appendix 4).**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **The informed consent addresses all biologic samples to be obtained in the SPRY protocol. If patients are appropriate for and agree to participate in substudies, they will then undergo the informed consent process for these sample collections.**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **All clinical data are collected from either the electronic health record or patient interactions and stored in the clinical research data repository managed by Biostatistical and Data Management Core in the Department of Critical Care Medicine at UPMC. Patient information that is shared with investigators beyond University of Pittsburgh or UPMC (i.e., the DSMB) will be shared as cumulative data when possible and de-identified to both maintain the integrity of the randomization blinding and protect the privacy of trial participants.** **For additional information on protected confidential data accessed by the SPRY-Application, please see the Digital Embedding section.**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **The investigators have no competing interests to report.**

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **The final dataset will be analyzed by the blinded trial collaborators and co-investigators at Berry Consultants, LLC who specialize in Bayesian statistical analysis and adaptive platform trial design. Data are shared only within the specifications of the a priori data sharing agreement. Data within the biorepository will be accessible by all trial investigators in compliance with Clinical Research Standards at University of Pittsburgh and as approved by the institutional review board.**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **The following information is provided within the informed consent document and will be followed if necessary:** **"If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation. You do not, however, waive any legal rights by signing this form."**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **The results of this trial will be published in a peer reviewed article following the completion of the trial. No personal results will be shared with the participants. No patient level data will be shared. Summarized data, as outlined in the Statistical Analysis Appendix, will be provided for future potential meta-analysis.** **In particular, treatment effects will be summarized from the model as a common odds ratio across surgical subtypes, as well as translated into expected mean differences in HFD for each surgical subtype enrolled in the trial. These treatment effect estimates will be from the Bayesian primary analysis model that allows for borrowing of information across doses and durations of the treatment. We will report raw mean (and SD) differences in HFD for each surgical subtype, under each dose and duration. These raw estimates will not take into account the borrowing of information across doses and durations and should be compatible with other trial publications for use in future meta-analyses.**
	31b	Authorship eligibility guidelines and any intended use of professional writers **Authorship guidelines will be followed based upon the journal accepting and publishing the trial results.**

	31c	Plans, if any, for granting public access to the full protocol, participant level dataset, and statistical code **Patient level data will not be shared publicly. The investigators may share the full protocol (if specifications beyond the published protocol manuscript are desired) and/or statistical code to provide result clarity and this will be considered on a case by case basis.**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **A sample consent form is provided as an appendix to this manuscript (Appendix 4).**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **In order to provide a library for future biological testing and sampling, SPRY-Metformin is creating a biorepository including a maximum of 5 blood samples (contact points 1, 3 [POD 0-3], and 4) throughout the trial (Figure 4). Patients discharged prior to POD 3 will have the fourth blood sample collected only if a venous blood sample is clinically indicated on the day of discharge. The biorepository includes the collection of peripheral blood mononuclear cells, plasma, and planned collections for DNA, RNA, and metabolomic analysis. Substudy patients will provide additional biorepository samples: microbiome (stool samples contact point 2, 3 [intraoperative rectal swab], 4, and 5) and muscle biopsy (contact point 3 [intraoperative] and contact point 6). Microbiome samples will be captured and preserved with the Zymo DNA/RNA Fecal Collection Kit (Zymo Research, Irvine, CA).**

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Statistical Analysis Appendix and Adaptive Design Report for SPRY-Metformin Domain

1.0 Introduction

SPRY-Metformin is a randomized control trial comparing the effectiveness of different doses and durations of metformin to placebo for nondiabetic patients with elective surgeries. In particular, we will evaluate 3 doses of metformin (500, 1000 and 1500mg) as well as 3 levels of pre-op duration of metformin (short, 7-28 days; intermediate, 29-90 days; and long, 90 days). Patients will be randomized to one of the three metformin doses or placebo but will not be randomized to the pre-op duration. Pre-op duration will be observed based on the timing of the first pre-op visit.

The primary endpoint to determine efficacy of metformin relative to placebo is hospital free days (HFD) at day 90 after the surgical encounter after administration of metformin vs. placebo. HFD at day 90 is an ordered categorical variable that takes on discrete integer values from -1 to 90 and is calculated as 90 minus the number of days of the index stay and the number of days readmitted within the 90-day time period following the surgical encounter. If mortality occurs within the 90-day time period, the patient is given an HFD value of -1 (ordered to be a worse outcome than being in the hospital for all 90 days).

There will be a maximum of 2000-2500 patients randomized in the trial. Within each of the 3 pre-op durations, patients will initially be randomized $\sqrt{3}$:1:1:1 to placebo and the 3 doses of metformin until a total of 500 patients have been randomized across all pre-op durations and followed for 90 days. Afterwards, interim analyses will occur sequentially after an additional 500 patients have been followed for 90 days. At each interim analysis, the trial can be stopped early for demonstrating efficacy of one of the metformin doses compared to placebo (see Section 3.1). If the trial has not stopped for success and continues enrolling, within each pre-op duration doses can be dropped for futility and responsive adaptive randomization will be used to randomize patients preferentially to the best performing metformin doses of all of the remaining doses within that pre-op durations (see Sections 3.2-3.3). The trial can stop enrolling patients within a pre-op duration if all metformin doses have been stopped within that duration for futility (see Section 3.2). Finally, at the interim when 2000 patients have been randomized across all pre-op durations and followed for 90 days, the maximum sample size could be increased from 2000 to 2500 (see Section 3.4).

2.0 Statistical Modeling

Inferences and quantities of interest used for response adaptive randomization, success or futility of metformin doses, and increasing the maximum sample size in this trial are based a Bayesian ordinal logistic regression model. The ordinal logistic regression model

accounts for underlying differences in the expected 90-day HFD distribution depending on surgical procedure or strata of the patient but assumes a common odds ratio treatment effect across the surgical strata. The odds ratio shift within an ordinal logistic regression model can be thought of similarly to an odds ratio within a logistic regression analysis of a dichotomous endpoint. Within ordinal logistic regression, we are simply performing multiple logistic regression analyses (one for each possible dichotomization of the data) and providing a weighted average of the odds ratios across these different dichotomizations. The assumption of a common odds ratio treatment effect across the different surgical subtypes translates into different absolute differences in the mean hospital free days within each surgical strata. For a common odds ratio across surgical strata, the larger the expected HFD within the strata the smaller the absolute mean difference in HFD between treatment and control.

In this setting, the Bayesian analysis makes use of non-informative prior distributions with regards to HFD distributions for each surgical strata and in this regard is very similar in nature to a frequentist ordinal logistic analysis. However, we chose to use a Bayesian analysis over a frequentist approach to allow for borrowing of information on the treatment effect across different doses and durations. This borrowing is done in the Bayesian setting by placing a hierarchical prior distribution on the treatment effects across all doses, all durations and the interactions between them.

2.1 Bayesian Ordinal Logistic Regression

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.

A Bayesian ordinal logistic regression model is used 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. 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:

$$Y_{c,i} \sim Bernoulli(\phi_{c,i}), c = 1 \dots 89;$$
$$logit(\phi_{c,i}) = \gamma_c + \mu_i;$$

where μ_i is a patient-specific mean function and γ_c is common across all patients.

The subject-specific mean function is as follows:

$$\mu_i = \alpha_{g(i)} + \theta_{t(i),d(i)}, i = 1 \dots N.$$

Within this model we assume that the underlying distribution of HFD is different within each stratum, g, and these differences across strata can be explained by a proportional log-odds ratio shift in the HFD distribution, α_g. 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 distribution $\theta_{t,d}$. Where a log-odds ratio $\theta_{t,d} < 0$ results in an increase in expected HFD. 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 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:

$$\theta_{t,d} = \beta_t + \kappa_d + \delta_{t,d}\ \ for\ t > 1, t = 1 \ldots 4, d = 1 \ldots 3.$$

Here, β_t is the log-odds ratio due to the dose, κ_d is the log-odds ratio due to the duration and $\delta_{t,d}$ is an interaction between dose and duration.

2.2 Model Priors

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

$$\pi \sim Dirichlet(\alpha_{-1}, \cdots \alpha_{90});$$
$$\gamma_c = logit\left(\sum_{i=-1}^{c} \pi_i\right), c = 1 \ldots 89;$$

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

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

$$\alpha_g \sim N(0, 2^2), g = 1 \ldots G.$$

Within pre-trial data (discussed in Section 4), the standard deviation of the log-odds ratios across surgical types/strata was estimated to be 1.5.

We assume a hierarchical distributions for the dose-effects and duration-effects each centered around a common mean so there is borrowing of information across doses and durations:

$$\beta_t \sim N(\mu_\beta, .5^2);\ \mu_\beta \sim N(0,1), t = 1 \ldots 4;$$
$$\kappa_d \sim N(\mu_\kappa, .5^2);\ \mu_\kappa \sim N(0,1), d = 1 \ldots 3.$$

Finally, we assume that the interaction between dose and duration has a normal prior distribution with mean 0 and standard deviation .2 to limit the amount of deviation of the overall effect, $\theta_{t,d}$, from the two additive effects.

2.3 Quantities of Interest

The following statistical quantities are used in the design of the trial and will be summarized at the conclusion of the trial. The posterior distribution of all model parameters is calculated using MCMC. The algorithm allows the generating of M (ex. 100,000) draws from the joint posterior distribution for all model parameters.

2.3.1 Summaries of Treatment Effect

The effect of each dose, *t*, and duration, *d*, will be summarized by reporting the posterior mean and 95% CI of the odds ratio, exp $(\theta_{t,d})$, (common across all surgical strata). Additionally, we will translate the posterior mean odds ratio into expected mean differences in HFD for each surgical subtype enrolled in the trial. Finally, we will report raw mean (and SD) differences in HFD for each surgical subtype, under each dose and duration. These raw estimates will not take into account the borrowing of information across doses and durations.

2.3.2 Probability beat placebo by CSD

To determine if a dose should be dropped within a duration or if we should increase the sample size at N=2000, we summarize the posteriority probability that each dose, *t*, and duration, *d*, of metformin is superior to placebo by some clinically significant difference (CSD). The CSD is defined as an odds ratio of .8. Thus, we are interested in the probability exp $(\theta_{t,d}) < .8$. This quantity is calculated from the M samples of the posterior distribution of the effect of each dose and duration, $\theta_{t,d}$, by reporting the proportion of posterior samples in which the odds ratio, exp $(\theta_{t,d})$ is less than .8:

$$\Pr\left(\exp\left(\theta_{t,d}\right) < .8 \mid \mathrm{Y}\right) = \frac{1}{M}\sum_{m=1}^{M}\left(\exp\left(\theta_{t,d}\right) < .8\right), t = 1 \ldots 4, d = 1 \ldots 3.$$

2.3.4 Probability of Optimal Dose within each Duration

Within a pre-op duration, we will use response adaptive randomization to allocate the next set of patients to all doses that have not been stopped for futility based the posterior probability that each dose is optimal within each pre-op duration. This quantity is calculated from the M samples of the posterior distribution of the effect of each dose within each duration, $\theta_{t,d}$, by reporting the proportion of posterior samples in which the log odds ratio for dose *t*, $\theta_{t,d}$ is the min observed effect across all three metformin doses *t=2:4* with duration *d*:

$$O(t,d) = \frac{1}{M}\sum_{m=1}^{M} I[\theta_{t,d} < \theta_{j,d} \; for \; all \; j \neq t], t = 1 \ldots 4, d = 1 \ldots 3.$$

2.3.5 Probability of Superiority

To determine if the trial should stop early for success at any interim or if the trial is successful at the final analysis, we summarize the posteriority probability that each dose of metformin is superior to placebo. For the superiority analysis, we estimate the effect of each dose of metformin by pooling across all actively enrolling durations. This is achieved by using the model described in Section 2.1 with the additional assumption that $\theta_t = \theta_{t,1} = \theta_{t,2} = \theta_{t,3}$. The posterior distribution of the pooled effect of each dose, θ_t, is this estimated by calculating M samples of the posterior distribution using only data from the actively enrolling doses within each duration. The probability of superiority of each dose relative to placebo is then calculated as the proportion of the M samples with θ_t less than zero:

$$\Pr(\theta_t < 0 \mid Y) = \frac{1}{M}\sum_{m=1}^{M} \theta_t < 0 \, , t = 1 \ldots 4.$$

2.4 Missing Data

All missing data will be imputed based upon the median observed 90-day HFD value for each treatment arm and preoperative duration. Sensitivity analyses will utilize the following different imputation strategies that do not assume missing at random (MAR):

- Impute all missing values as the median observed 90-day HFD value under the placebo group.
- Impute all missing values as the worse observed 90-day HFD value within that surgical strata.

2.5 Heterogeneity of Treatment Effects

The heterogeneity of treatment effects across different key patient subgroups will be explored by allowing the common odds ratio per dose and duration, exp ($\theta_{t,d}$), to be subgroup dependent. Subgroups of interest include: Surgical specialty (see Table 4.1), operative stress level as defined by the Operative Stress Score,[1] surgical subtype, age category, and frailty based upon the prospectively calculated Revised Analysis Index.

3.0 Interim Analyses and Trial Adaptations

Before interim analyses begin, patients will be randomized √3:1:1:1 to placebo and the three doses of metformin within each pre-op duration. Interim analyses will then begin when 500 total patients across all doses and durations are randomized and have been followed for 90 days and will continue after every additional 500 patients have been

followed for 90 days. Thus, there are 4 total interims at 500, 1000, 1500, and 2000 patients with 90-day follow-up and a final analysis when 2500 patients have been followed for 90 days. At each interim we allow the following adaptations:

- Success
- Dose / Duration Dropping
- Response Adaptive Randomization

3.1 Success

Success will be declared at an early interim or at the final analysis, and the trial will stop if the posterior probability of superiority of any dose of metformin relative to placebo defined in Section 2.3.3 is greater than a pre-defined interim-specific threshold. The thresholds for each interim are reported in Table 3.1.1 and are based on an O'brien Fleming spending function assuming a maximum sample size of 2500:

Table 3.1.1: Success Thresholds

Analysis	**500**	**1000**	**1500**	**2000**	**2500**
Success Threshold	***.9999***	***.9999***	***.9985***	***.9950***	***.9894***

3.2 Dose / Duration Dropping

Metformin doses will be dropped within a duration based on the probability of futility defined in Section 2.3.1. Specifically, for dose *t* in duration *d* if

$$\Pr\left(\exp\left(\theta_{t,d}\right) < .8 \mid \mathrm{Y}\right) < .15, t = 1 \ldots 4, d = 1 \ldots 3;$$

dose *t* will be dropped in duration *d* and patients within that duration will no longer be randomized to that dose.

We require an additional order restriction on dose dropping so that a dose must be dropped first in the short duration, then the intermediate duration then the long. Therefore, a dose cannot be dropped in the intermediate duration until it has first been dropped in the short and cannot be dropped in the long duration until it has first been dropped in the short and intermediate.

Enrollment to a pre-op duration will be stopped if all doses within that duration have been stopped and the trial will stop for futility if all pre-op durations have been stopped.

3.3 Response Adaptive Randomization within Durations

Within each pre-op duration of metformin, we will use response adaptive randomization to allocate patients to the most optimal dose of metformin within that pre-op duration. Initial randomization is set to $\sqrt{3}$:1:1:1 to placebo and the 3 doses of metformin within each duration. This allocates approximately .366 percent of the patients to placebo. This percentage allocation to placebo will be maintained throughout the course of the trial. However, after the first interim analysis, the remaining .634 percent of patients will be allocated to metformin doses within each duration that have not been dropped for futility and preferentially based on the probability that the dose is optimal within the duration defined in Section 2.3.2 and renormalized over the currently enrolling doses.

3.4 Increasing maximum sample size to 2500

At the interim analysis when 2000 patients are randomized and followed for 90 days the maximum sample size will increase to 2500 if at least one dose within one pre-op duration meets the following criteria:

$$\Pr\left(\exp\left(\theta_{t,d}\right) < .8 \mid \mathrm{Y}\right) > .50, t = 1 \ldots 4, d = 1 \ldots 3.$$

After 2000 patients have been randomized and are waiting to be followed for 90 days, enrollment will continue until the interim analysis takes place. If the above criteria is met, enrollment will continue to a maximum of 2500. If the above criteria is not met, enrollment will stop.

4.0 Clinical Trial Simulations

Clinical trial simulations are used to provide example trial results, to optimize clinical trial design (best thresholds for early success, dose dropping, and futility stopping) and to determine the sample size needed within this trial to obtain at least 80% power for a clinically meaningful treatment effect and a one-sided 2.5% type I error under the null distributions. Simulations were provided under a wide range of clinical trial parameters to optimize the design with the design team. Operating characteristics are provided for the final design herein.

To create realistic clinical trial simulations, we obtained pre-trial data from patients within the UPMC electronic health records who had received an in-patient elective surgery and met the additional inclusion/exclusion criteria:

- Inclusion:
  - Age > 60 or RAI > 30 or CCI >2
  - Surgery performed in either PUH or SHY hospitals
- Exclusion:
  - Diabetes or previous metformin use
  - Had one of the following surgery types:
    - Minimally invasive cholecystectomy
    - Irrigation and debridement of a wound
    - Hyst. Total abdomen

- Vaginal Hyst.
- Sleeve Gast.

This resulted in data from 16,932 patients across 376 surgery types. Table 4.1 provides summaries of the data by clustering each surgery type into one of 14 surgical specialties. In particular, for each surgical specialty we report: total number of patients, total number of surgical types, mean and median HFD, and 90-day mortality rates.

Table 4.1: Summary Pre-Trial Data

	Total N	Surgical Procedures/ Strata	Mean HFD	Median HFD	Mort. Rate
Total	**16832**	**376**	**79.5**	**86.0**	**0.05**
ORTHO	3849	72	83.2	87.0	0.03
SPINE	2884	25	83.6	87.0	0.02
CARDIAC	1979	34	75.5	83.0	0.07
GENERAL	1692	52	70.9	82.0	0.10
UROLOGY	1221	21	85.2	88.0	0.01
THORACIC	1130	35	76.7	84.0	0.06
NEURO	1099	35	78.0	87.0	0.08
VASCULAR	1043	39	77.7	86.0	0.07
HPB	729	16	78.6	84.0	0.03
COLORECTAL	707	20	77.0	84.0	0.04
ENT	334	8	79.6	86.0	0.04
TRANSPLANT	136	8	71.0	81.5	0.01
GYNE	15	7	80.1	86.0	0.07
BARIATRIC	14	4	73.3	80.0	0.07

4.1 Virtual Patient Simulation

Within each simulation, we assumed that the SPRY trial would enroll subjects from all strata that had at least 50 subjects in the pre-trial data (77 total) with the proportion of patients within each enrolling stratum estimated from the pre-trial data. We also assume that the HFD distribution per strata under placebo is the same as what was observed in the pre-trial data. Finally, we assume treatment effects for each metformin dose can be summarized as a common percent reduction in the mean hospital days (HD) across all strata. This treatment effect is assumed to be 0% for all null scenarios and a maximum of 15% for all alternative scenarios.

The trial was powered assuming a common treatment effect of 15% reduction in mean hospital days across all surgical subtypes. The common treatment effect is specified as a percent reduction in mean hospital days to help elicit the minimal clinically meaningful treatment effect from the trial design team. The reduction of 15% in hospital days is thought to be the minimal clinically meaningful treatment effect within this patient population. This common percent reduction across surgical subtypes, results in different absolute effects in mean hospital days depending on the surgical subtype (see Table 4.2). In particular, for one of the most common surgical subtypes of Total Knee Arthroplasty, this would result in a half of a day reduction in hospital days (3.4 days in hospital vs. 2.9

days). In comparison, under Endovascular aortic repair, the expected reduction in hospital days is 1.6 (10.8 days in hospital vs. 9.2 days). A percent reduction that that is at least 15% would result in a savings ranging from 0.2 – 3.9 hospital days for the 10 most common surgical types.

To obtain a common percent reduction in mean HD across all strata within our simulations, we find the strata-specific odds ratio shift under treatment relative to the empirical HFD distribution under placebo that results in the assumed common percent reduction in HD per strata.

For example, Figure 4.1 plots the assumed HFD distribution under placebo and under a 15% reduction in HD for the most common surgical type, Total knee arthroplasty. Within the pre-trial data there were 1115 patients who received a total knee arthroplasty. The empirical HFD distribution observed in the pre-trial patients and assumed for placebo within this stratum is plotted in blue with approximately 10% of patients having 89 HFD, 35% with 88 HFD and 29% with 87 HFD. Across all patients, the mean HFD is 86.6. To achieve a treatment effect of a 15% reduction in HD (plotted in green) we would need an odds ratio shift in the treatment distribution relative to placebo of .62. This would result in a mean reduction in HD of .5. This would shift approximately 15% of patients under treatment to 89 HFD, 42% to 88 HFD and 25% to 87 HFD.

Similar summaries for the 10 most common surgical types are provided in Table 4.2.

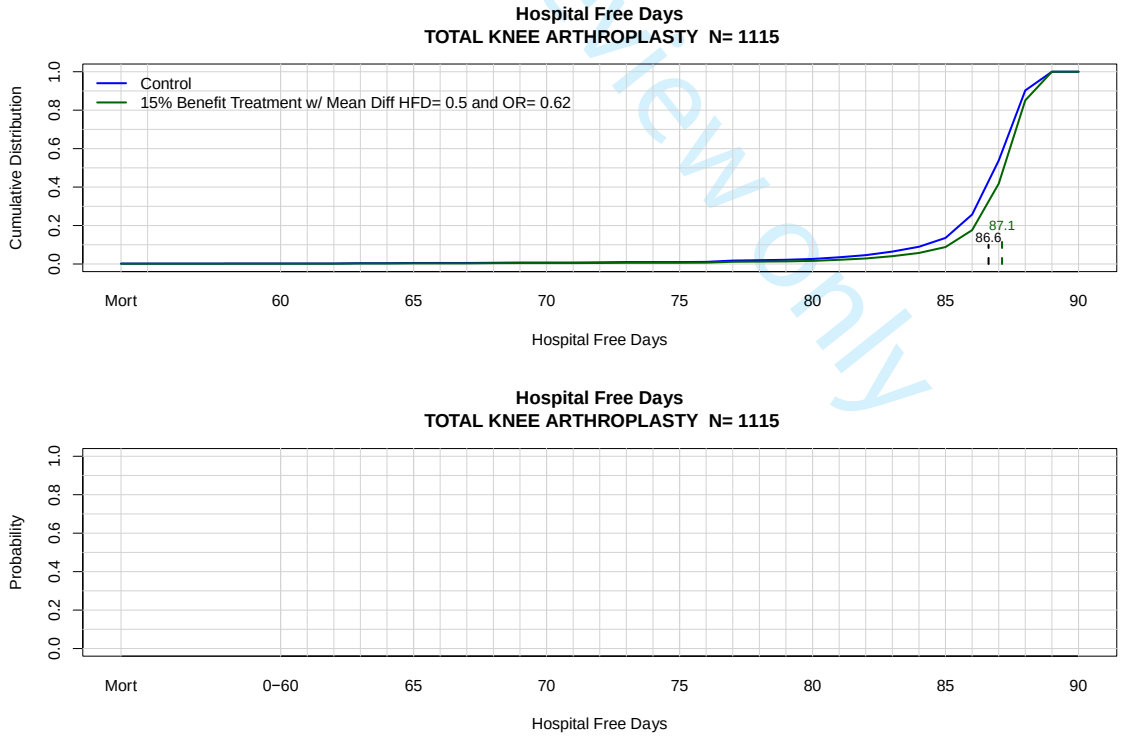

Figure 4.1: Example Strata-Specific HFD distribution under placebo vs. treated with a 15% reduction in HD for Total Knee Arthroplasty.

Table 4.2: Summary of Control Distributions and Treatment effects for 10 most common surgical types.				
	Prop. Overall	**Mean HFD Control**	**Mean Diff. Under Common 15% Reduction in HD**	**Odds-Ratio Shift Under Common 15% Reduction in HD**
Total Knee Arth.	0.08	86.6	0.5	0.62
Spine Post. Fuse Internal Fix.	0.07	82.8	1.1	0.71
Total Hip Arth.	0.05	85.6	0.7	0.72
Endo. Aortic Valve Replace	0.03	79.2	1.6	0.78
Spine Ant. Cervical Dissect. and Fuse	0.03	86.2	0.6	0.77
Spine Post. Lumbar or Thoracic	0.03	84.7	0.8	0.77
MIS Partial Pulmonary Lobectomy	0.02	83.2	1.0	0.73
Prostatectomy Lap. Robotic Assist.	0.02	88.6	0.2	0.50
Laparotomy	0.02	64.1	3.9	0.76
Total Hip MIS 2 Incisions	0.02	88.0	0.2	0.76

5.0 Example Trials

We provide example data and results for two simulated example trials. In particular, for each interim in each example trial we provide a plot of the data and results (ex. Figure 5.1.1). Each plot shows the following:

- Top Left: Allocation to each dose and the number of patients within each duration for each dose.
- Top Middle: Mean estimates (circles) and CI for the ORs for each dose and duration of metformin as well as pooled for each dose (above the P and in grey) across all actively enrolling durations. The confidence intervals show the lower .15 quantile so that if the lower bar goes above .8 the dose may stop for futility and the upper Xth quantile where X is interim specific success threshold based on the success rules provided in Table 3.1.1 so that if the upper bar goes below 1 for the pooled estimate, the dose will be declared a success. Raw OR values are provided plotted as stars.
- Top Right: The new allocation probabilities within each duration for placebo and the 3 metformin doses.
- Bottom: Cumulative probabilities of observing each HFD value or less for Placebo and each dose of metformin averaged across all durations and separately within each duration. As the curves move down and to the right, the expected HFD is increasing and the number of expected HD is decreasing.

5.1 Example Trial 1

Figure 5.1.1 shows results from the first interim analysis when 500 patients have 90-day data. Approximately 200 patients have been allocated to placebo and 100 to each of the 3 metformin doses. Estimates for the OR of all doses (500, 1000 and 1500) given at the short duration are 1.2 or greater, all have a posterior probability that the OR < .8 less than 15%, and all are stopped for futility. Thus, the trial stops enrolling in the short duration. All doses are still enrolling in the medium and long durations. Within the intermediate duration the 1500mg dose has an OR estimated around .75, and the 1000 and 500mg have an OR estimated around .85. Therefore, the new allocation probabilities are weighted towards the 1500mg dose within the intermediate duration. Within the long duration the 1500 and 1000mg doses have an OR estimated around .6 and are preferentially allocated to over the 500mg dose which has an estimated OR of .85.

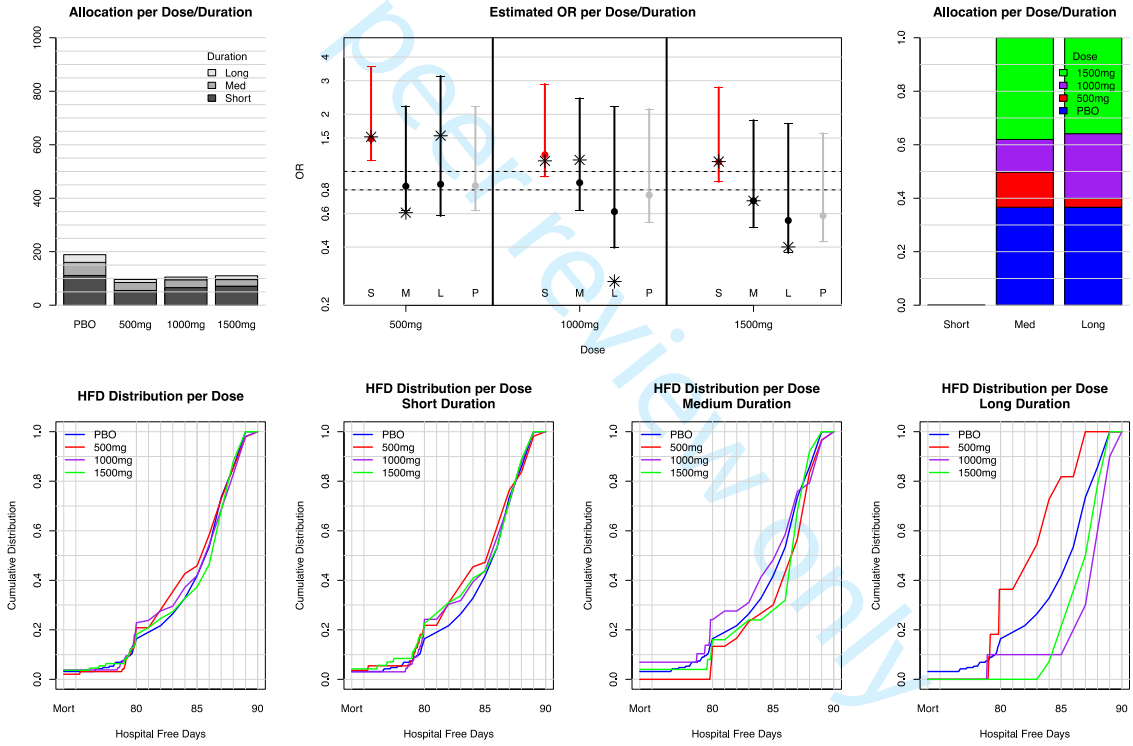

Figure 5.1.1: Example Trial 1; Interim N=500

Figure 5.1.2 shows results from the second interim analysis when 1000 patients have 90-day data. Approximately 375 patients have been allocated to placebo, 150 to 500mg, 200 to 1000mg and 300 to 1500mg. No new patients have been enrolled in the short duration. Within the intermediate duration the 1500mg dose has an OR estimated around .70, and the 1000 and 500mg have an OR estimated around .90. Therefore, the new allocation probabilities are weighted towards the 1500mg dose and away from the 1000 and 500mg dose within the intermediate duration. Within the long duration the 1500mg and 1000mg doses have an OR estimated around .65 and .75 respectively and are preferentially allocated to over the 500mg dose which has an estimated OR greater than 1. The 500mg dose in the long duration has less than a 15% posterior probability of having an OR < .8. However, it is not stopped since the intermediate duration has not stopped yet for this dose.

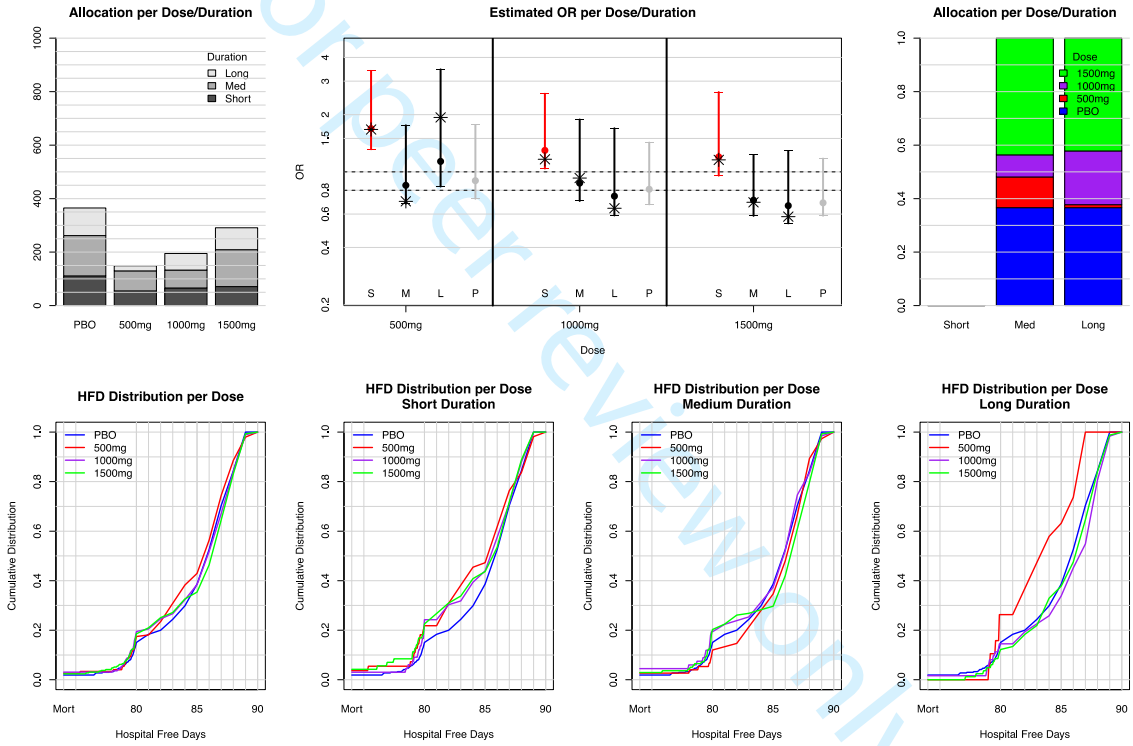

Figure 5.1.2: Example Trial 1; Interim N=1000

Figure 5.1.3 shows results from the third interim analysis when 1500 patients have 90-day data. Approximately 550 patients have been allocated to placebo, 200 to 500mg, 250 to 1000mg and 500 to 1500mg. No new patients have been enrolled in the short duration. The 500mg dose is stopped in both the intermediate and long durations. Within the intermediate and long durations, the 1500 and 1000mg doses have an OR estimated around .80 and have approximately equal allocations within each duration.

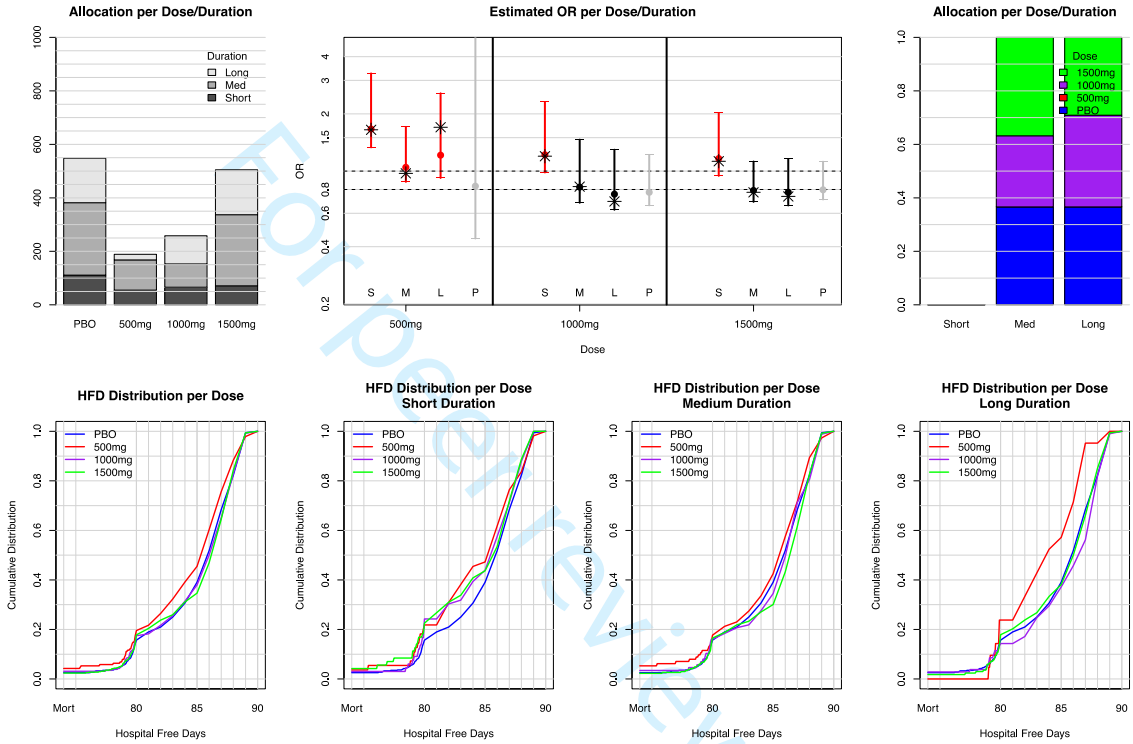

Figure 5.1.3: Example Trial 1; Interim N=1500

Figure 5.1.4 shows results from the fourth interim analysis when 2000 patients have 90-day data. Approximately 725 patients have been allocated to placebo, 200 to 500mg (no new patients), 425 to 1000mg and 675 to 1500mg. No new patients have been enrolled in the short duration. The pooled estimate across all actively enrolling durations (intermediate and long) for the 1000mg dose is approximately .75 and the upper limit of the CI has dropped below 1. Therefore, the posterior probability that the OR<1 for the 1000mg dose is greater than the interim-specific threshold (.995) and the study is stopped for success.

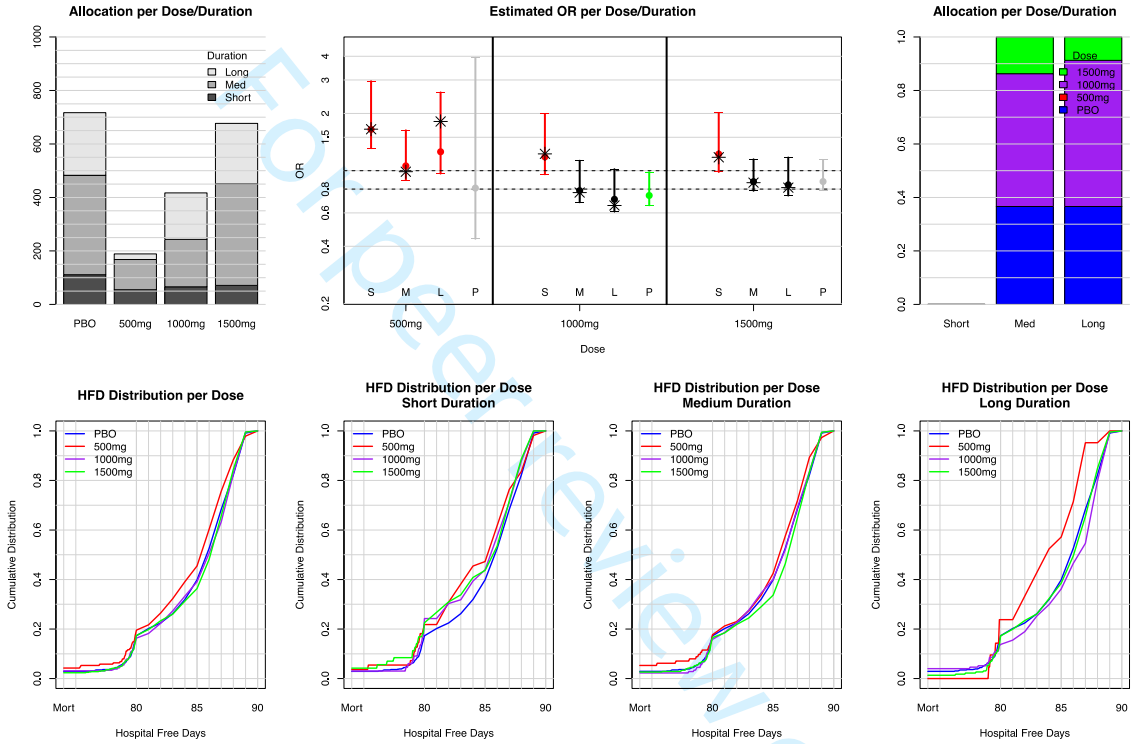

Figure 5.1.4: Example Trial 1; Interim N=2000

5.2 Example Trial 2

Figure 5.2.1 shows results from the first interim analysis when 500 patients have 90-day data. Approximately 200 patients have been allocated to placebo and 100 to 500, 1000 and 1500mg each. Within the cumulative distribution plots, the curves for each dose of metformin within each duration are mostly to the left and above the curve for placebo, indicating less HFD for each dose in each duration relative to placebo. For all doses within all durations the OR is estimated to be greater than 1.3 and the posterior probability that the OR < .8 is less than 15%. Thus, the trial stops for futility at the first interim analysis.

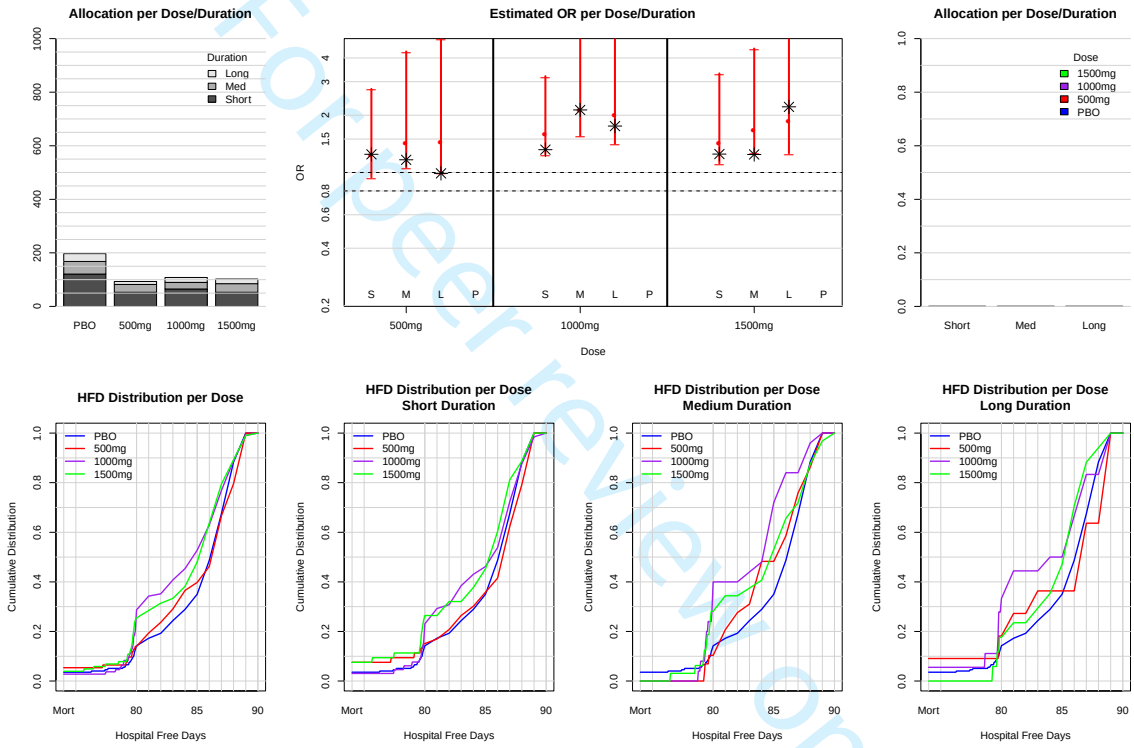

Figure 5.2.1: Example Trial 2; Interim N=500

6.0 Operating Characteristics

We simulate clinical trials under 7 possible treatment effect scenarios. Under the null scenario we assume that there is a 0% reduction in HD across all doses and all durations of metformin. Under all other scenarios we assume that the max effect is a 15% reduction in HD. The effect for each dose and duration is specified based on the dose-response and duration-response assumptions. We simulate under 3 different dose-response profiles. Under the "plateau" dose-response profile we assume a 7.5% reduction of the 500mg dose and a 15% reduction for the 1000 and 1500 mg doses. Under the "one good" profile we assume that there is a 0% reduction in HD for the 500 and 1000mg doses and a 15% reduction for the 1500mg dose. Under the "linear" profile, we assume a 3.75% reduction in HD for the 500mg dose, a 7.5% reduction for the 1000mg dose and a 15% reduction for the 1500mg dose. We also simulate under 2 different duration-response profiles, one where all durations work equally well and one where the intermediate and long durations work equally well but the short duration does not work for all doses. For each simulation we assume that 40% of the patients will have a short duration, 35% an intermediate duration and 25% a long duration.

Under each treatment effect scenario, we simulate 1000 clinical trials and report the following operating characteristics in Table 6.1:

- Probability of early success and total success
- Mean number of subjects enrolled in the trial
- Probability of stopping the short duration, intermediate duration or all of the durations
- Probability each dose is selected as best
- Probability increase sample size to 2500

The overall Type I error of the trial is 2.4% with 1% of the null trials stopping early for success and 91% of the null trials stopping early for futility or not increasing to the maximums sample size of 2500. The mean number of patients enrolled under the null scenario is 676. The probability the sample size is increased to 2500 under the null is 8%.

The power of the trial under the alternative scenarios ranges from 77-92% with the mean number of patients enrolled ranging from 1725 to 1822. When the short duration does not work, the probability of stopping the short duration is 80-84%. Across all alternative scenarios, we are choosing the right dose (a dose that has the maximum 15% reduction in HD effect) 79-96% of the time. Finally, the maximum sample size is increased from 2000-2500 21-31% of the time.

Table 6.1: Operating Characteristics

Dose Response	Duration Response	Prob. Success		Mean N	Prob. Stop Futility			Prob. Selected Best			Prob. Enroll 2500
		Early	Total		Short	Int.	All	500	1000	1500	
Null	-	0.010	0.024	676	0.95	0.92	0.91	0.35	0.30	0.35	0.08
Plateau	**All Work**	0.75	0.92	1767	0.12	0.06	0.04	0.04	0.50	0.46	0.21
	Not Short	0.66	0.87	1822	0.86	0.15	0.09	0.06	0.44	0.49	0.26
One Good	**All Work**	0.67	0.86	1729	0.28	0.15	0.11	0.03	0.03	0.95	0.23
	Not Short	0.56	0.78	1725	0.83	0.28	0.19	0.06	0.04	0.90	0.26
Linear	**All Work**	0.64	0.84	1776	0.20	0.12	0.10	0.04	0.10	0.86	0.26
	Not Short	0.51	0.77	1782	0.82	0.24	0.17	0.07	0.14	0.79	0.31

Subject ID: _____

SAMPLE: SPRY Clinical Research Form

SPRY-Metformin 30 Day Assessment

Interviewer: Please complete before start of the interview. Enter subject ID # on the top of every page *Follow up telephone call attempts will be made for the contact using discretion and judgment of the LTO personnel.*	
Date of SPRY Enrollment (MMDDYY)	
Date of Study Surgery (MMDDYYYY)	
Date of current interview (MMDDYYYY)	
Interview conducted with:	☐ Subject ☐Surrogate/LAR If Interview conducted with surrogate, please indicated reason: ☐subject too ill/in a medical facility☐ Subject Death (Date: ___/___/_____) ☐Other _____

Hello, I am [*NAME*] calling from the SPRY Study that you agreed to participate in prior to your surgical procedure. I'm calling you today to see how you are doing and to conduct the survey with you for the study.
Is this a good time? We anticipate the total time for this call to be about 10-15 minutes.

If no: "When is the best time to reach you? Do you have a preference what time of day we call?"
If yes: Wonderful. First let me remind you a bit about the purpose of the study

Purpose: The purpose of this study is to test how well different doses and durations of the study medication "Metformin" may improve how people without diabetes do after having their surgical procedure. Today I'm just going ask you some questions about any medical services you may have used following your surgery as well as some questions about your use of the study medication and how you are feeling in general.

Section 1: Post-discharge Resource Use

Interviewer: **If patient not yet discharged from surgical hospital, skip to Section 2**

1. When you were discharged from the hospital following your surgery, did you go home right away or did you first stay **overnight in a different hospital or medical facility**?
   - ○ Home (subject's normal domicile i.e. nursing home, assisted living, group home)
   - ○ Home with medical assistance (home health care)
   - ○ Another hospital or medical facility (new to subject)
   - ○ Other: _____
   - ○ Don't Know
   - ○ Not discharged from surgical hospital

Subject ID: _____

○ Refused to answer

Interviewer: **[if "Home"] proceed to Question 3**

2. [If discharged to [Another Hospital or Medical Facility] to which type of facility did [patient's name] go after hospital discharge (choose all that apply if patient has been sent to multiple facilities since discharge from surgical hospital)?

○ Total Days admitted _____

Another Hospital	☐ 1	# admt___ Total Days_____
Rehabilitation Center	☐ 2	# admt___ Total Days_____
Hospice (hospice facility)	☐ 3	# admt___ Total Days_____
LTAC	☐ 4	# admt___ Total Days_____
SNF	☐ 5	# admt___ Total Days_____
Other (*specify*)_____	☐ 6	# admt___ Total Days_____
Don't Know	☐	
Refused	☐	

3. Since being discharged to home, have you been admitted to a hospital OVERNIGHT? *(Do not include an overnight stay in the emergency room.)*

○ Yes
○ No
○ Don't know
○ Refused to Answer

4. [If yes] What was the name(s) of the hospital(s) to which you were readmitted?

_____
_____
_____

○ Don't Know
○ Refused to answer

Subject ID: _____

Section 2: Quality of Life

Interviewer : Now I will ask you questions about your general health. Please indicate which statements best describe your own health today.

Mobility

□ I have no problems walking
□ I have some problems walking
□ I am confined to bed

Self-Care

□ I don't have problems caring for myself
□ I have some problems washing or dressing myself
□ I can't wash or dress myself

Usual Activities (like work, housework, family activities)

□ I don't have problems performing my usual activities
□ I have some problems performing my usual activities
□ I can't perform my usual activities

Pain and Discomfort

□ I don't have pain or discomfort
□ I have moderate pain or discomfort
□ I have extreme pain or discomfort

Anxiety and Depression

□ I am not anxious or depressed
□ I am moderately anxious or depressed
□ I am extremely anxious or depressed

PART TWO

Now, on a scale from 0 to 100, where 100 represents the best imaginable health while 0 represents the worst possible health you could imagine, at what number would you rate your health in general **now? (Interviewer, mark number on scale to the right and write the number given by the subject)**

Answer: _____

Subject ID: _____

Interviewer: Now I'm going ask you some questions about your current employment status. We are interested in whether you have recovered from your recent surgery and hospitalization sufficiently to return to work or your usual activities. Please choose the answer that most closely describes your situation right now

Right now, my work and/or usually activity is:

- Full-time employment ❑
- Part time employment ❑
- Homemaker ❑
- Retired ❑
- Unemployed due to disability or illness ❑
- Unemployed due to job loss and/or inability to find work ❑
- Student ❑
- Other ❑
- Unknown (proxy response) ❑

This work and/or usual activity is:

- The same as before my surgery ❑
- Different from before my surgery due to effects from the surgery ❑
- Different from before I was hospitalized, but not due to my surgery ❑
- Unknown (proxy response) ❑

Subject ID: _____

Section 3: Use of Study Medication

Interviewer: I am now going to ask you some questions about your use of the study medication.

1. **Since your discharge from the hospital following your surgery, have you temporarily or permanently stopped taking your study medication at any time?**
   ❑Yes, Temporarily _____(# of days stopped) ❑Yes, permanently _____ (date stopped)
   ❑ No

2. **Since your discharge from the hospital following your surgery, are there any days or times that you missed or forgot to take your study medication?** ❑ Yes ❑ No

3. **(If yes) How many doses of your study medication would you say you missed or forgot to take since you were discharged from the hospital after your surgery? _____ (# of doses)**

End of Interview: Thank you for your time today. As a reminder, there is one final follow-up call/visit for this study which takes place in approximately 2 months from now. Would you be able to schedule that call/visit now?
(If a telephone follow-up): The call will take approximately 30 minutes and we'll ask you similar questions to today's call with some additional questions surrounding your memory and thinking.
(If in person follow-up): We estimate the time of the visit to be approximately 1.5 hours where we will do some tests of your thinking as well as your physical function. The visit will take place in our Critical Care Offices in Oakland.

University of Pittsburgh
School of Medicine
Department of Critical Care Medicine

600 Scaife Hall
3550 Terrace Street
Pittsburgh, PA 15261
Fax: 412.647.8060

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

STUDY TITLE: Strategies to Promote ResiliencY (SPRY)-An Adaptive Randomized Clinical Trial of Metformin in High Risk Surgical Patients

PRINCIPAL INVESTIGATOR:
Dr. Matthew Neal
University of Pittsburgh
Departments of Surgery, Critical Care Medicine, and the Clinical and Translational Science Institute
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200 Lothrop Street
Pittsburgh, PA 15213
Phone: 412.647.1158

Tamera Means, MD, MHS
Clinical Research Coordinator
412.383.1573

SOURCE OF SUPPORT: UPMC Internal Funds

KEY INFORMATION:

You are being invited to consider joining a research study. Participation in a research study is always voluntary. The first part of this form is a summary of the study. Please also read the Detailed Information section that follows before making a decision about participation in this study.

Why are researchers doing this study?
Increasing age is a risk factor for having complications after surgery. There are some

studies suggesting metformin, a medication often used for diabetes, may be able to reduce inflammation as well as have other effects which may help with complications.

In this study, we want to look at whether or not metformin is able to improve your outcome and reduce complications after elective surgery.

What is involved in this study?
You will be randomly assigned to receive one of 3 doses of metformin (500 mg, 1000 mg, or 1500 mg) or one of three doses of placebo (sugar pills). You will take this study drug starting tomorrow and continue to take this study drug for 90 days after your surgery.

If you participate in this study, you may have blood samples taken at up to 5 timepoints while you take the study drug. This blood would be stored without identifiers.

You may also complete questionnaires during this study.

What are some reasons I might choose to volunteer?
Researchers are conducting this study because they do not know if metformin might be helpful. Their goal is to determine what might help future patients.

What risks are involved in the study?
For those people who are assigned to take metformin, some people may experience mild stomach and digestive system side effects as outlined in the 'Potential Risks and Discomforts' section which follows. These are usually temporary and resolve with continued use of metformin.

Other minor risks are noted in the 'Potential Risks and Discomforts' section.

What other things should I consider?
You will not be charged for costs associated with the study drug or for any procedures required by the study. Costs associated with your routine medical care, including your elective surgery and hospital stay, will still be your responsibility or that of your insurance provider.

Will being in this study help me?
For those assigned to the placebo group, no direct benefit is expected. For those who will be taking metformin, it is not known if there will be any direct benefit to you.

What are my choices if I decide not to be in this study?
If you decide not to join the study, this will have no effect on your elective surgery.

DETAILED INFORMATION

INTRODUCTION:

This study is being conducted to determine if people taking metformin have better outcomes and fewer complications after having elective surgery compared to people not taking metformin. Metformin is a medication commonly given by doctors to reduce blood sugar in people with diabetes (a disease where you have higher than normal blood sugar). The use of metformin in this research study is investigational. "Investigational" means that the use of metformin for the purpose of improving outcome after surgery is not approved by the United States Food and Drug Administration.

In this consent form, "you" and "your" always refers to the subject and "we" always refers to the study team.

You are being asked to participate in this research study as you are scheduled for an elective surgical procedure in a UPMC facility as part of your routine care. You may be eligible for participation in this research study if you are at least 60 years of age and do not have diabetes. You may also be eligible if you are younger than 60 years of age and have certain chronic medical conditions. Women enrolled into this study must be post-menopausal, which means that you have not had a menstrual period within the last 12 months.

DESCRIPTION OF THE RESEARCH

A total of up to 2,000 men and women may be enrolled into this research study over the next two years at the University of Pittsburgh/UPMC.

Your study participation will begin on the day you are seen in the clinic for the pre-operative evaluation prior to your surgery. As part of this study, you will take a study drug prior to your operation and then for ninety (90) days after the date of your surgery. Medical record information may be collected for approximately a year after your completion of the study drug.

WHEN THE INVESTIGATOR IS ALSO THE CARE-PROVIDER:

For some of you, your physician is involved as an investigator in this research study. Before agreeing to participate, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your physician.

STUDY PROCEDURES:

If you decide to take part in this research study, certain research procedures may occur.

Clinic Visit Before Your Surgery:

- You may answer questions regarding your demographic details (date of birth, race, etc.)
- You may answer a few general questions about your medical history, allergies, and your use of alcohol to verify that you are eligible to participate in this study.
- You may be asked to provide contact information (name, phone number, mailing address, e-mail address) for you, your spouse/partner, and maybe for another friend/relative. This contact information is collected as the study team may need to contact you throughout the study. If the study team cannot reach you, they would then try to reach one of the other individuals you have identified for the study team.
- You may have a blood sample drawn. Blood will be drawn to store some blood for future testing to be able to compare how aspects of your blood change as you progress through the study. The blood would likely be drawn by putting a needle into a vein in your arm. About four (4) tablespoons of blood may be taken for this study at the same time as blood is drawn for testing required for your surgery if needed. Your blood would be drawn by a nurse or another skilled medical professional. The blood draw should take about ten minutes. Other blood samples may be taken at other times during the study. When possible, these blood samples would be drawn at the same time as standard of care blood is drawn.
- You will be randomly assigned by chance to receive one of the following study drugs to take one time daily by mouth:
    - 500 mg (1 pill) metformin extended release (ER)
    - 1000 mg (2 pills) metformin extended release (ER)
    - 1500 mg (3 pills) metformin extended release (ER)
    - Placebo (1 pill)
    - Placebo (2 pills)
    - Placebo (3 pills)

A placebo is a sugar pill that looks like a metformin pill but does not contain any active drug. At the beginning of the study, an individual has a 37% (37 in 100) chance of receiving placebo and a 63% (63 in 100) chance of receiving one of the three metformin doses. Once an individual is assigned to receive placebo or metformin, the individual takes this study drug for the duration of the study.

As this study is designed to enroll people over 2 years, the likelihood that those who participate at a later time will receive metformin or placebo will change based on the number of individuals who have participated in the study up to that point.

If you are assigned to either the 1500 mg metformin extended release dose or the 3 pill placebo option, you will take 2 pills for the first 7 days. Starting on day eight, you will then take 3 pills. The reason to begin with the lower dose is that this will help to reduce possible side effects if you are taking metformin.

Both you and the study team will not know if you are taking metformin or placebo during the study. In the event of an emergency, it is possible for the study team to learn what study drug you are taking.

You should start to take the study drug the morning after your pre-operative clinic visit. You should take the study drug every day. You should take the study drug with food to minimize GI effects. You should bring your current study drug pill bottle with you on the date of your surgery. Depending upon when your surgery is scheduled, the UPMC Investigational Drug Service may need to send you additional study drug by mail. It is important that you take all of the study drug in the current study drug pill bottle before starting to take study drug from a new study drug pill bottle received in the mail.

You should continue to take the study drug through the day of your elective surgical procedure and for 90 days following the date of your surgery. The study drug will only be available to you during the study.

- You will be given a wallet card that indicates that you are participating in this study. This card lists that you may be taking metformin. You should carry this wallet card with you and show this wallet card to any health care professional you see while you are taking the study drug.
- We may contact your PCP and other members of your health care team to let them know of your involvement in this study. These communications could occur at various times throughout your study participation.
- As part of the process for you to decide to participate in this study, you will speak with one of the investigators involved with this study. If the investigator cannot promptly come to your clinic location, this interaction may occur via phone or via remote video conference. The purpose of your conversation with the investigator is for the investigator to ensure that you understand what is involved in study participation and to ensure all of your questions have been answered. Following the conversation with the investigator, either in person or by telephone/video conference, this informed consent will be signed by you and by the investigator. A copy of the informed consent will be given to you.

These research procedures will likely take place in the clinic where you are having your office visit before surgery. The research procedures may add approximately 45 minutes to your visit.

Prior to the day of surgery, ideally within 48 hours of study enrollment:

- You may receive a phone call from a member of the Long Term Outcomes Core team. The purpose of this phone call is to remind you of the importance of

bringing your study drug pill bottle with you when you come to the hospital for your elective surgery.
- During this phone call, a member of the Long Term Outcomes Core may ask you some questions about your general health and to assess your thinking and memory. This phone call should take about 15 minutes.

Day of surgery:

- You should give your study drug pill bottle to hospital staff personnel when you arrive at the hospital for your surgery. Your study drug pill bottle will be kept by hospital personnel while you are in the hospital. You will continue to take the study drug while you are in the hospital.
- You may have a blood sample drawn from the intravenous (IV) line that is inserted in your arm for your surgery or directly from a vein. About four (4) tablespoons of blood may be taken. Your blood would be drawn by a nurse or another skilled medical professional. The blood draw should take less than ten minutes.
- We may review your medical records and collect information related to your surgery and the medications you receive for your surgery as well as your general health. We may continue to review and collect this kind of information while you are in the hospital.

These research activities should take about 25 minutes.

After surgery:

- You may have blood drawn from the intravenous (IV) line that was inserted in your arm for your surgery or directly from a vein. About three and a half (3.5) tablespoons of blood may be taken at this time. Your blood would be drawn by a nurse or another skilled medical professional. The blood draw should take less than ten minutes and should occur in your hospital room.

During your hospital stay:

- You will continue to receive the study drug during your hospital stay. We may decide to suspend giving you the study drug if you have certain types of difficulties as a result of your surgery.

Day 3 after surgery or immediately prior to hospital discharge if earlier than Day 3:

- You may have blood drawn from the intravenous (IV) line inserted in your arm for your medical care or directly from a vein. About three and a half (3.5) tablespoons of blood may be taken at this time. Your blood would be drawn by a nurse or another skilled medical professional. The blood draw should take less than ten minutes.

Day of hospital discharge:

- You should be given another pill bottle containing the same study drug as before your surgery. You should continue to take the study drug for a total of 90 days since the date of your surgery.

These research procedures should take about 15 minutes and would take place in your room at the hospital before you leave the hospital to go home.

Follow-up visit approximately 2-3 weeks after surgery (Usual Care):

- You may have blood drawn from a vein in your arm. About three and a half (3.5) tablespoons of blood may be taken for this study. Your blood would be drawn by a skilled medical professional. The blood draw should take about ten minutes and would take place in the clinic where you see your doctor or in a nearby UPMC location.

Phone call 30 days (+/- 7 days) after surgery:

All subjects participating in this study may receive a phone call from the Long Term Outcomes Core who may ask you questions about your general health, your taking of the study drug, your general level of physical activity, and about whether you have seen any doctors/been to the hospital since your surgery. This phone call should take about 10-15 minutes.

Phone call 90 days (+ 28 days) after surgery:

If you are not participating in the Motor Assessment Group (see below), the Long-Term Outcomes Core may contact you via telephone to ask you the same kinds of questions as asked during the 30-day call. You may also be asked some questions to assess your memory, attention, and thinking skills.

This phone call should take about 30-35 minutes.

For those subjects who completed their 90 day questionnaires via phone call with the Long Term Outcomes Core, you will be reminded to discard the wallet card.

MOTOR ASSESSMENT GROUP

For those subjects who live within 20 miles of Oakland and are over the age of 65, you may be asked to come in to the offices of the Department of Critical Care Medicine in Oakland to be a part of a Motor Assessment Group. Being a part of the Motor Assessment Group would been an in-person visit at 90 days (+28 days after surgery) rather than a phone call.

The goal of the Motor Assessment Group is to determine if people taking metformin have differences in their muscle strength after surgery compared to people not taking

metformin. The Motor Assessment Group could enroll approximately 670 subjects.

During this visit, members of the Long Term Outcomes Core may ask you similar questions to those asked during the phone call 30 days after surgery. You may also be asked some questions to assess your memory, attention, and thinking skills.

In addition, you may have your grip strength measured and be asked to walk as far a distance as you can walk on a 50-foot (out and back) course in 2 minutes.

These interactions should take approximately 90 minutes.

During this visit, you will be reminded to discard the wallet card.

If the study team should determine that these questionnaires would be best collected via a phone call rather than via an in-person visit, a phone call would be scheduled with you to complete these questionnaires.

MICROBIOME SUB-STUDY

We are interested to determine if there are differences in the microbiome (the microorganisms such as bacteria and their genetic material that are present in or on the human body) for people who are taking metformin as compared to people who are taking placebo. In order to determine these differences, up to 1000 subjects may be asked to provide stool specimens as part of a Microbiome Sub-study.

Clinic visit before your surgery:

- You may be asked to provide a stool specimen prior to your surgery. You would be instructed on how to collect a stool specimen at home. We would give you instructions and a container, which is placed on your toilet, so you can collect the stool. You will place a small amount of stool in a special tube. You would be given a pre-paid envelope to mail the sample back to the study team for processing and storage. If you are asked to provide a stool specimen prior to your surgery, you will be asked to provide other stool samples at other times during the study.

Day of surgery:

- You may have a rectal swab collected. Once you have been taken to the operating room and given medications for your surgery to make you sleepy, a cotton swab would be gently inserted approximately 1 inch into your anus. The cotton swab would be gently swirled for 15-30 seconds and then removed. The swab may be sent to the study team for processing and storage. The purpose of collecting the rectal swab is the same as collecting stool specimens.

During your hospital stay:

- You may be asked to provide a stool specimen during your hospital stay. The stool specimen would be collected in the same way as the previous time. If you need help to collect the stool specimen, a nurse, another medical professional or study team member may assist with the collection. The stool would be placed in a special tube and sent to the study team for processing and storage in the same way as the previous specimen.

  If you may not have a bowel movement in the hospital, you may be asked to provide a stool specimen from your first bowel movement following discharge from the hospital. If you had a bowel movement in the hospital, but stool specimen collection did not occur, you may be asked to provide a stool specimen from your next bowel movement following discharge from the hospital. You are asked to collect the stool specimen within 5 days of your surgery. You would be provided with a pre-paid envelope to mail the sample back to the study team.

Day of hospital discharge:

- We will provide you with the materials needed for the collection of another stool specimen before you leave the hospital as well as a pre-paid mailing envelope to return the stool sample to us.

Post-op clinic visit:

- We would like you to collect a stool specimen as close as possible to the time of the follow-up visit with your doctor (approximately 2-3 weeks after your surgery). You would follow the same procedure as before to collect the stool specimen.

MUSCLE BIOPSY SUB-STUDY

Up to 200 of the subjects who take part in the Motor Assessment Group who are willing will be recruited to participate in the Muscle Biopsy Sub-study. We are interested to determine the effect metformin may have on muscle structure and on muscle cell functioning. In order to do so, we will collect samples of muscle tissue from up to 200 subjects who are participating in the Motor Assessment Group at two time points of the sub-study. We will compare the results with the results from strength testing completed as part of the Motor Assessment Group (Visit at 90 days (+ 28 days) after your surgery).

A sample of muscle may be obtained at up to 2 timepoints during this sub-study:

- While you are under anesthesia on the day of your elective surgery
- While you are awake during the Visit at 90 days (+ 28 days) after surgery. This muscle biopsy will occur in Radiology Procedure Unit B (RPU B) or on the 8th Floor of UPMC Montefiore Hospital, Translational Research Center

You will be given instructions on withholding certain medications which thin the blood or slow clotting time if you are prescribed them and agree to undergo the biopsy.

The muscle sample collection procedure involves using a needle to take a small piece of muscle tissue from the outside of your upper leg, about 4-6 inches above the knee. The skin will be cleaned and injected with local anesthetic (numbing medicine) 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 (about the size of a pea) 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.

Muscle biopsies would be performed by physicians on the study team experienced in muscle biopsies.

Your clinical care team will address biopsy care needs while you are in the hospital and you will be given post-biopsy care instructions for the 90-day biopsy.

CONTINUED ACCESS TO MEDICAL RECORD INFORMATION

We also would like to have permission to collect medical record information for over one year from the time you stop taking the study drug. We would collect information related to your general health such as test results, treatments, and doctor's notes as well as information about any hospital admissions and emergency department visits. In order to collect this medical record information from non-UPMC facilities, you may be asked to sign a separate authorization which would permit the sharing of your non-UPMC protected health information with the study team.

DATA RETENTION/BLOOD, STOOL, AND MUSCLE BIOPSY SAMPLES

All of the blood samples, stool samples, and muscle biopsy collected during this study will be placed in a specimen bank. The purpose of the specimen bank is to collect and store these samples for future research studies related to aging as well as to study various types of diseases and conditions. Your blood samples, stool samples, and muscle biopsy samples, as applicable, will be kept forever. Your past, current and future medical record information stored at UPMC will be available to be matched with your biological samples. This data will be stored in a controlled-access database. Your data, which may include your health information, your biological samples, and genetic data generated from your samples will be stored with a unique ID number, but will not be stored with your name. Your blood samples, stool samples, and muscle biopsy samples, as applicable, may be used by other investigators here at the University of Pittsburgh and UPMC and may be shared with other researchers, industry, or with a federal repository without additional consent from you. One collaborator who may receive a portion of your muscle biopsy samples is the University of Utah. Your muscle biopsy samples will not be stored long term at the University of Utah. When your biological samples are shared, they will be shared without identifiers. Data and samples may be shared for any research question.

It is also possible a portion of your muscle biopsy sample may be analyzed immediately

by investigators at the University of Pittsburgh.

Research data will be maintained for at least 7 years following closure of this research study.

Analysis of these samples may include genetic analysis as previously described.

Any genetic information obtained from these studies will not be entered into your medical records. No clinically relevant results will be returned to you.

As the research questions to be asked are unknown and as the meaning and significance of the results of any future unspecified testing of the biospecimens collected under this research study is unknown, personal results will not be disclosed to research subjects.

Your blood samples, stool samples and research data collected in this study may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products. You will not retain any property rights, nor will you share in any money that the investigators, the University of Pittsburgh, or their agents may realize.

POTENTIAL RISKS AND DISCOMFORTS

Metformin: The known risks are effects on your stomach and digestive system such as gas, loss of appetite, nausea, vomiting, diarrhea, and decreased levels of B12 (cobalamin).

These side effects are usually temporary and resolve with continued use of metformin.

There is a rare risk of something called lactic acidosis. This is the build-up of something called lactate in your blood. Lactate in your blood normally is harmful if there too much. Early signs of this are changes in your breathing and belly pain. Always call the study team if you have any concern.

You should not participate in this study if you know you have an allergy to metformin.

As with all medications, in very rare cases, the use of metformin may result in an allergic reaction. Some symptoms of allergic reactions include: rash, difficulty breathing, wheezing, sudden drop in blood pressure, swelling around the mouth, throat or eyes, a fast pulse, sweating. Please seek emergency treatment immediately if you experience these kinds of symptoms and then alert the study doctor and study staff if you have these symptoms as a very serious allergic reaction may be life-threatening.

The study drug could interact with other drugs such as carbonic anhydrase inhibitors,

gliptins, and cimetidine.

Blood sampling: You may experience temporary discomfort, bruising, pain at the blood draw site, and fainting (rare risk).

Surveys/questionnaires: Individuals completing questionnaires/surveys may experience mild frustration or boredom in completing these assessments.

Motor Assessment Group:

Two-minute walk test: You may become tired during this test, depending upon your general health. If you become tired, you may stop walking at any time.

Grip strength test: There are no known risks.

For Microbiome Sub-Study:

Stool sample: There are no known risks to providing a stool sample.

Rectal swab: The collection of the rectal swab may cause temporary mild discomfort following the procedure.

For Muscle Sub-Study:

Muscle sample collection: You may have pain, bleeding, bruising at the site of the incision. In rare cases, infection at the site of the muscle sample collection is possible. Some people may also faint at the sight of needles or blood. To minimize this risk, we would perform this procedure while you lie down. Careful sterile technique and local anesthesia should reduce the likelihood of any of these complications. The risk of pain during the muscle collection procedure is very small, because we will give you anesthesia (numbing medicine). In case, you feel anything more than pressure, you will tell us, and we would give you more numbing medicine until the area is completely numb. People experience the feeling of a muscle biopsy differently because of different pain thresholds and how the numbing medicine works in any individual. You may feel very little or only a charley horse sensation, or you may feel more distinct pain. After the study, you have a chance of experiencing soreness at the site of muscle sample collection for 24 to 48 hours. However, over-the-counter medications such as Tylenol and cold packs are enough to control such a discomfort. There is also a very rare possibility of numbness around the site of muscle sample collection. This is typically temporary and should resolve within a few months. The muscle sample collection may leave a scar approximately long like this dash "__".

Lidocaine use with the 90-day muscle biopsy: Minor pain at the injection site and

brief stinging may occur. A possible side-effect is an anaphylactic reaction (a severe allergic reaction to the Lidocaine) that could result in symptoms such as shortness of breath, swelling of the throat, inflammation of the skin, skin rash, low blood pressure and death (rare).

Breach of confidentiality: It is possible that someone could find out that you were in this study and could find out information about you. Every effort will be made to prevent this from happening. To protect your confidentiality, we will remove your name and other personal identifiers from the samples and from the medical record information we obtain. This information will be identified by a code.

Risks associated with gene studies: The risks associated with gene studies include the potential for a breach of confidentiality which could affect future insurability, employability, or reproduction plans, or have a negative impact on family relationships and/or result in paternity suits or stigmatization.

In addition, there is a Federal law, called the Genetic Information Nondiscrimination Act (GINA), that generally makes it illegal for health insurance companies and group health plans to use genetic information in making decisions regarding your eligibility or premiums. GINA also makes it illegal for employers with 15 or more employees to use your genetic information when making decisions regarding hiring, promoting, firing, or setting the terms of employment. This new Federal law does not protect you against genetic discrimination by companies that sell life, disability, or long-term care insurance.

To facilitate communication during the study, this study will use e-mails to update the study team of your progress in the study. This may include the use of your name and other personal identifiers to ensure accurate information. Although every reasonable effort has been taken, confidentiality during Internet communication activities cannot be guaranteed and it is possible that additional information beyond that collected for research purposes may be captured and used by others not associated with this study.

As with any experimental procedure, there may be adverse events or side effects that are currently unknown and certain of these unknown risks could be permanent, severe or life-threatening.

ANTICIPATED BENEFITS TO SUBJECTS

For those subjects assigned to the placebo group (no metformin will be taken), no direct benefit from study participation is expected. For those subjects who will be taking metformin, it is not known if there will be any direct benefit to you from being in the research study.

ALTERATIVE TREATMENTS

There are no alternative procedures which may be of benefit to you if you choose not to participate in this research study.

NEW INFORMATION

You will be promptly notified if any new information we learn during this research study may cause you to change your mind about continuing to participate in the study.

COSTS AND PAYMENTS

If you agree to take part in this research study, you and/or your insurance will not have to pay for the study drug or any tests that are being done only for the research study. However, you are still responsible for paying for elective surgery and hospital admission as well as other care you would normally receive. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

If you complete the entire study, you may be paid up to $200 in return for your time and effort associated with research study involvement. These funds will be provided to you as $50 payments 4 times throughout the study:

$50 following the clinic visit before surgery
$50 following the hospital stay
$50 following the phone call at roughly 30 days after surgery
$50 following the phone call/visit at roughly 90 days after surgery

In addition, if you participate in the Microbiome Sub-study, you will be paid $20 for each of the stool samples and rectal swab collected for this study for a total of $80 over the course of the study.

You will receive this compensation via a reloadable debit card. The debit card is not loaded with funds until you coordinate with the study team to load the card with funds. Since you are being compensated for your participation in this study, your name, address, and social security number will be released to the Accounting Office. If you are not comfortable with providing your social security number for use by the Accounting Office, taxes will automatically be removed from the payment.

USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

We are also requesting your authorization or permission to review your medical records. This research study may involve the recording of past, current and/or future identifiable medical information from your hospital and/or other (e.g. physician office) records to determine whether you meet the conditions for participation in this study. The information that may be recorded will include information concerning your medical history, results of lab tests, diagnostic procedures, the reason for your elective surgical procedure, and the type of medical insurance you have. In addition, medical record information related to your hospital stay for your elective surgery and any follow-up visits may be recorded to assess the effects of the study drug. As part of this research

study, some information that we obtain from you may be placed into your medical records held at UPMC, including the results of any testing performed specifically for this research study. This authorization to provide identifiable information available to members of the study team is valid for an indefinite period of time.

In addition to the Principal Investigator listed on the first page of this consent form and the other investigators involved in this study and the study team, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

- Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office for the purpose of monitoring the appropriate conduct of this research study.
- Authorized representatives of UPMC or other affiliated health care providers for the purpose of (1) fulfilling orders made by the investigators for hospital and health care services (e.g., diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (e.g., quality assurance).

We will protect your privacy and the confidentiality of your records, as described in this document, but cannot guarantee the confidentiality of your research records, including information obtained from your medical records, once your personal information is disclosed to others outside UPMC or the University.

In addition, coded data about your participation in this study will be shared with Berry Consultants, LLC, a collaborator, and an external Data Safety and Monitoring Board (DSMB). The DSMB will review this coded data for the purpose of overseeing study progress and evaluating the potential risks to subjects associated with study participation.

We may send your de-identified muscle biopsy samples for analysis to investigators at the University of Pittsburgh and/or to other collaborators such as the University of Utah for analysis. The linkage document containing your name and your study ID will not be shared with these research teams. Descriptors such as your age and gender may be shared but no identifiable information.

We may share your responses from the EQ-5D questionnaires with your health care providers.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

MEDICAL CARE FOR RESEARCH RELATED INJURY

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation. You do not, however, waive any legal rights by signing this form.

VOLUNTARY PARTICIPATION

Your participation in this research study is entirely voluntary. You may want to discuss this study with your family and friends and your personal physician before agreeing to participate. If there are any words you do not understand, feel free to ask us. The investigators will be available to answer your current and future questions.

Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

To formally withdraw your consent for participation in this research study, you should provide a written and dated letter of this decision to the principal investigator of this research study at the address listed on the first page of this form.

RIGHT TO WITHDRAW

It is possible that you may be removed from the research study by the researchers if, for example,

- You do not or cannot take the study drug properly.
- The researcher feels it is in your best interest not to continue in the study.
- The funding for the study is not continued.
- There may be other reasons to remove you from the study not identified at present.

In the event of study withdrawal, you will be asked to return the study drug pill bottle to the study team using a pre-paid mailing envelope.

Upon your withdrawal from this study, you should participate in additional monitoring follow-up procedures that are being conducted to measure the safety of the study drug.

All information obtained from you up until the date of your withdrawal from the study will be maintained in a coded fashion. No further data will be collected following your withdrawal from the study. Your blood and stool samples which have been placed into storage may continue to be used for analysis, but no further samples will be collected from you for this study.

VOLUNTARY CONSENT TO PARTICIPATE:

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator listed on the first page of this consent document at the telephone number given.

I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator. I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that occurred during my participation. By signing this form, I agree to participate in this research study and provide my authorization to share my medical records with the study team. A copy of this consent form will be given to me.

_____

Printed Name of Participant

_____ _____ _____

Signature of Participant Date Time

INVESTIGATOR CERTIFICATION:

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions, concerns or complaints as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____

Printed Name of Person Obtaining Consent Role in Research Study

_____ _____ _____

Signature of Person Obtaining Consent Date Time

CONSENT FOR OPTIONAL GROUPS AND SUB-STUDIES

You are being asked to confirm your interest in participating in the following optional groups and sub-studies which have been explained in the preceding pages:

Initials of person obtaining informed consent indicating Group/Sub-study is available*	**Title of Group/Sub-Study**	**Initials of this subject indicating their interest in Group/Sub-study***
	Motor Assessment Group (involves in person visit around 90 days after surgery instead of phone call and involves grip strength and two-minute walk tests)	
	Microbiome Sub-study (involves stool sample collections and rectal swab)	
	Muscle Biopsy Sub-study (involves up to 2 muscle biopsies)	

*** Initials are required in both the first and third column for Sub-study participation.**