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$\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. **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).**

References

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