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PILOT STUDY: The metabolic and genetic drivers of body composition changes following weight loss surgery

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Log of Protocol Changes

DATE OF AMENDMENT REQUEST	VERSION #	REQUESTED CHANGE	DATE OF APPROVAL
8/20/2025	1.2	Initial Approved Version	08/21/2025
9/29/2025	1.4	i) Provide Invitation Letter in person ii) Amend description of DXA and Indirect Calorimeter procedures iii) Extend visit windows iv) Change screening requirements from U&E to Basic Metabolic Panel v) Allow collection of License Plate information for study visits.	10/7/2025
5/5/2026	1.6	Change of PI and record storage	5/14/2026
6/1/2026	1.7	i) Addition of video consenting ii) Removal of metabolic arm iii) Workflow amendment to allow for visit flexibility iv) Increased BMI v) Removed Waist to hip circumference measurement vi) Inclusion of participants undergoing Endoscopic Sleeve Gastrectomy	6/14/2026
8/26/26	1.8	i) Remove wording on using medical questionnaire to determine eligibility ii) Remove recent blood donation as exclusion factor iii) Add in basal cell carcinoma as exception for history of cancer	

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator:*

Signed: Emily Lantz Date: 05/20/2026

Name: Emily Lantz, PhD
Title: Assistant Professor

** The protocol should be signed by the local investigator who is responsible for the study implementation at his/her specific site; i.e., if Investigational New Drug study, the individual who signs the Form FDA 1572.*

1.0 Background

Since its inception, bariatric surgery has helped thousands of morbidly obese patients achieve dramatic and prolonged weight loss, with approximately 280,000 US patients estimated to undergo the procedure annually (2). However, due to surgical changes in the gut anatomy and ensuing reductions in food intake, patients are at heightened risk of protein malnutrition. Despite aggressive efforts to maintain adequate protein intake post-procedure, most patients experience a degree of muscle wasting, with ~57% meeting the criteria for sarcopenic obesity 2 years post-surgery (3), compromising overall muscle function and quality of life. Compounding this issue further, prolonged weight loss is not achieved in all patients, with as many as 20-30% of patients undergoing bariatric surgery failing to meet expected clinical benchmarks of successful weight loss post procedure (excess weight loss <50% or BMI >35; (4)). These latter individuals, experiencing diminished muscle mass but persistently elevated body mass, are at heightened risk of functional impairment and disability. There is therefore a *critical need* to **i)** understand the drivers of muscle loss post-bariatric surgery, and **ii)** develop predictors for failed weight loss in these individuals.

We have previously shown that the ability of exogenous amino acids to stimulate the synthesis of muscle contractile proteins, an essential process in the maintenance of muscle mass and function, is diminished with obesity (**Fig. 1A**; (1)), with the magnitude of impairment inversely related to the degree of adiposity present (**Fig. 1B**; (1)). Further, we have been able to mimic the anabolic desensitizing effect of obesity on muscle to amino acids in both lean individuals (**Fig. 1C**; (5)) and cultured muscle cells (**Fig. 1D**; unpublished data), demonstrating the direct and potent suppressive effect of increased cellular lipid availability on muscle protein anabolism. Given that fat mass remains substantially elevated in bariatric surgery patients for months to years post-surgery (6), our work suggests that these patients likely experience a prolonged period of diminished muscle anabolic sensitivity to digested nutrients. Coupled with the known challenge of maintaining adequate protein intake post-surgery, we postulate that these patients face a dual insult, compounding the challenge of protecting muscle mass post-procedure and underscoring the high observed rates of sarcopenia. In response, we plan to establish whether bariatric surgery patients suffer from systemic anabolic resistance post-procedure and how this relates to the development of muscle wasting and impaired contractile function. Establishing muscle anabolic resistance as a contributory factor to the development of muscle wasting post-gastric bypass surgery will enable the advancement of appropriate nutritional, exercise, and pharmacological mitigating strategies.

An individual's genome, foregut transcriptome, and gut microbiome have all been implicated in influencing weight status in the wider population (7-9). To our knowledge, the impact of a patient's genetics and microbiome on weight loss outcomes after bariatric surgery has yet to be established. Data from the literature has shown associations between weight loss and mutations in genes including PKHD1 (high expression in the exocrine pancreas) and SLCO3A1 (expressed mainly in the cerebral cortex), but these genotypes have proven to be rare (10). However, mouse models have previously shown an association of gastrin-related pathways in stomach mucosa and obesity that persisted across obesity-susceptible genotypes, suggesting a dominant effect of the local environment (11). Prior collaboration

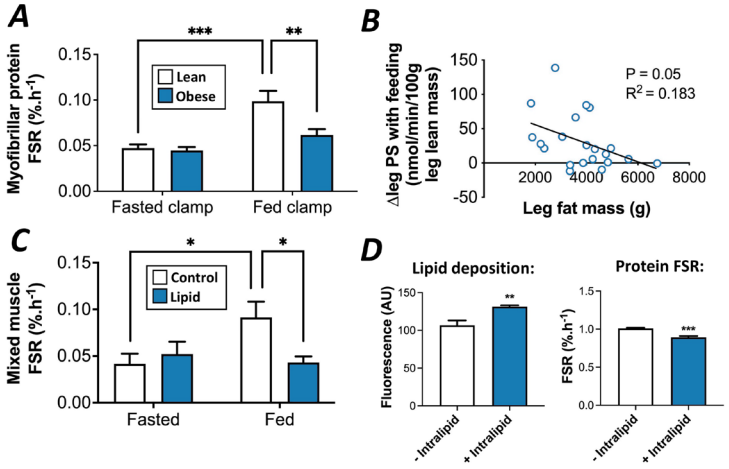


Figure 1: Impact of Class I obesity on muscle protein kinetics. *A) ability of hyperaminoacidemia to stimulate muscle myofibrillar protein synthesis rates is blunted in obese vs. lean older men. B) The ability of exogenous amino acids to stimulate leg protein synthesis rates is inversely proportional to leg adiposity. Data reported as means +/- SEM. * P<0.05; ** P<0.01; *** P<0.001. Adapted from (1).*

between the UTMB Department of Surgery and UTMB's Assay Development Service Division (ADSD) investigators established a robust relationship between mucosal gene expression patterns and histologic findings in gastro-esophageal reflux disease (GERD). From a list of more than 100, a refined subset of 10 genes was shown to have the ability to identify changes of intestinal metaplasia. Combining the expertise of our team members, we expect to be able to identify gene expression profiles associated with post-bariatric surgery outcomes.

Collectively, we propose a pilot study that will utilize cutting-edge stable-isotope methods to precisely delineate the impact of obesity and bariatric surgery on whole-body protein kinetics, avoiding the costly, invasive, and time-consuming procedures required to study muscle protein kinetics directly. Coupled with interrogation of the individuals' gut transcriptome, microbiome, diet, activity, body composition, and energy expenditure, our work will provide the most comprehensive evaluation of the impact of bariatric surgery on metabolic events pivotal for the maintenance of muscle mass performed to date. Moreover, our work has the potential to develop a weight loss prediction model for bariatric surgery patients based on stomach mucosa gene expression or gut microbiome that could help guide patients and their clinicians on the most appropriate weight loss treatment strategy.

2.0 Rationale and Specific Aims

Our *long-term* goal is to develop effective treatment approaches that can minimize the loss of muscle mass following bariatric surgery without compromising weight loss potential or patient recovery. Our *overall objectives* in this pilot application, which are the next step towards the attainment of our long-term goal, are to:

i) Establish the presence of anabolic resistance to exogenous amino acids in gastric bypass patients and determine its relationship to the loss of muscle function and mass.

ii) Identify predictors for the failure to maintain weight loss post-bariatric surgery.

The *rationale* for this project is that confirming the presence of anabolic insensitivity to dietary amino acids post-surgery would provide the necessary scientific framework for a program of work aimed at delineating the causes for this phenomenon and establishing effective treatment solutions that could resensitize muscle to nutrient availability, thereby averting sarcopenia development. It also offers the potential of identifying biomarkers that can be used to detect patients unlikely to benefit from bariatric surgery.

To address the study's objectives, the following two specific aims will be pursued:

1. Establish the impact of Class III obesity and gastric bypass on exogenous amino acid utilization, protein intake, physical function, and lean mass.

2. Examine the association between a patient's gut transcriptome and microbiome on energy intake, energy expenditure, and weight loss following bariatric surgery.

3.0 Inclusion/Exclusion Criteria

Subjects must meet all the inclusion criteria to be eligible to participate in the study. A subset of individuals will undergo an additional battery of tests which have further inclusion and exclusion criteria, as detailed below

Inclusion criteria are:

Bariatric Surgery Group (SURGERY)
Age: 18 to 65 years at time of consent
BMI: 35-65 $kg.m^{-2}$
Seeking to undergo bariatric surgery (including Endoscopic Sleeve Gastroplasty) at UTMB
All races and ethnic backgrounds
Ability to speak and read English (*)
Subject has provided informed consent in a manner approved by the IRB and is willing and able to comply with the trial procedures.

(*) The study procedures (e.g. at-home collection and processing of biological samples, completion of dietary questionnaires), requires sound written and spoken English.

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

Exclusion Criteria are:

Bariatric Surgery Group (SURGERY)
Fails the medical criteria for bariatric surgery (†).
Anemia (hematocrit < 33 %)
Recent (5 years or less) history of cancer with the exception of basal cell carcinoma
Systemic steroids or immunosuppressant use for 8 or more consecutive days in the past 6 months, or any use of anabolic steroids or growth hormones in the same period.
Body mass index < 35 or > 65 $kg.m^{-2}$.
Acute infectious disease or chronic infection.
Pregnancy or breast-feeding.
Any medical condition that, in the opinion of the investigator, would place the subject at increased risk for participation.
History of prior non-compliance that would, in the opinion of the investigator, make it difficult for the subject to comply with the study procedures or follow the investigator's instructions.
Concurrent participation in another research study.
Use of an investigational agent in the 30 days prior to signing informed consent.

(†) Bariatric surgery patients routinely undergo a comprehensive medical examination, including assessment of their cardiovascular and pulmonary systems, to determine their fitness for surgery and general anesthesia. Medical clearance for bariatric surgery will be utilized as an assessment of medical fitness for participation.

4.0 Enrollment /Randomization

The study is not a treatment trial. Participants will not be randomized to a treatment.

5.0 Study Procedures

Recruitment methods: We will recruit the following:

> *SURGERY:* We will recruit up to 100 individuals approved to undergo bariatric surgery at UTMB to establish the relationship between weight loss and the patients' gut transcriptome and surgery type

(sleeve gastrectomy or gastric bypass). Patients will be provisionally screened against study criteria by clinic staff, with individuals appearing to meet the criteria sent a study invitation letter via MyChart (**Appendix I**) prior to attending a standard pre-op clinical visit at the Metabolic & Bariatric Surgery Specialty Clinic, UTMB's League City campus or in-person by a member of the clinical staff. The staff members performing the initial screen will be restricted to those already involved in the patient's care. Individuals expressing an interest in the study will receive a detailed oral description of the study from the Investigators either at their next clinical visit, or by telephone/video call, depending on their preference. This may include a video overview of the study that would be provided to interested participants to watch. Consent will be collected at the same visit from participants expressing an interest to complete the paperwork on the same day (many participants travel long distances to attend their clinic visit at UTMB League City). Individuals will be able to request to have a separate consent visit on a different day if that is their preference. No study procedures, except the medical questionnaire (see below), will be performed for at least 48 hours following the collection of consent to provide participants with a cooling off period, in addition to their right to withdraw at any stage.

All individuals will be provided with the opportunity to have their questions regarding the study addressed. Those wishing to participate will be asked to sign a consent form.

Medical Screening:
Within 6 weeks following the collection of informed consent, participants will undergo medical screening to confirm that they meet the stated eligibility criteria.

- For participants in the SURGERY Group, the comprehensive medical assessment performed for individuals to be cleared for bariatric surgery will be used in lieu of a separate visit.

A medical history in addition to measures of blood pressure, a complete blood count (CBC) and Basic Metabolic Panel will be inspected in the medical record (SURGERY). Only lab values recorded in the past 6 months at time of inspection of the medical record will be considered – the same time frame utilized for bariatric surgery clearance. If records in this time frame are not available, a blood sample will be collected and the relevant tests performed, as would be necessary for them to proceed with their elective surgery. In addition, all participants will be sent a medical questionnaire (**Appendix III**) The questionnaire may be administered in hard copy or electronic form (REDCap).

Below follows a description of the visits and procedures performed once medically cleared to participate (see Figure 2).

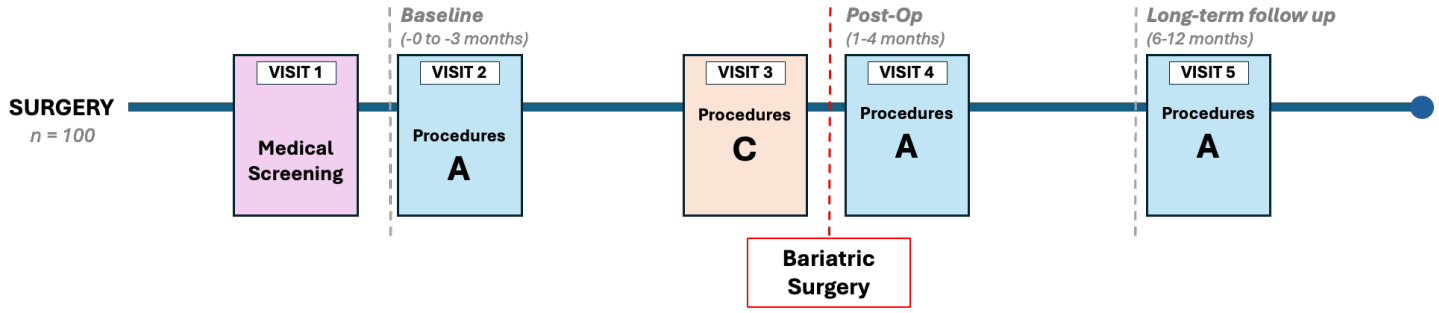


Figure 2: Overview of study protocol

NOTE: To accommodate patient, facility, and staff availability, visits within each time window may not occur in the stated order. For example, Visit 3 may proceed Visit 2.

	Procedures A	**Procedures C**
	SURGERY	*SURGERY*
Location	Metabolic & Bariatric Surgery Clinic, UTMB, League City	Outpatient, UTMB, Clearlake
Procedures	Record the following SoC measures: 1) Anthropometry 2) Handgrip strength 3) 24 hr Dietary recall	Gut transcriptome analysis
Length of each visit (*)	60 min (SoC)	10 min

(*) Length denotes the time added for research procedures on top of standard clinical care; SoC: Standard of Care

A description of each of the above procedures follows.

PROCEDURES A:
SURGERY: VISITS 2, 4, & 5

The following procedures are considered SoC and performed routinely in bariatric surgery patients when they attend the Metabolic & Bariatric Surgery Specialty Clinic at the League City campus. These measures may occur across multiple visits to accommodate clinic staff availability, but the time burden for patients or number of procedures performed will not be affected by project enrollment. Equally, the data may be collected retrospectively if the clinic visit has already occurred prior to study enrollment. We will collect the data for the below parameters when they attend their regularly scheduled visits.

Handgrip strength: Handgrip strength will be recorded using a portable handheld device. The participant will be instructed to rest the elbow of their dominant arm at 90° and maximally squeeze the plates of a handgrip dynamometer. This will be repeated several times with a short rest (~1 min) between each attempt. If the participant is unable to perform the procedure using their dominant hand for any reason, attempts will be made to record the handgrip strength of their non-dominant hand.

Anthropometric measures: Attempts will be made to record the following variables: body weight, and body fat and lean mass. The latter will be measured by bioelectrical impedance analysis (MC-580 TANITA or equivalent). Electrical bioimpedance will not be performed in individuals that exceed the weight limit of the device (600 lb).

Twenty-four-hour food intake recall: Patients will meet with a Registered Dietitian and asked to recall their food and drink intake over the previous 24 h period.

PROCEDURES C:
SURGERY: VISIT 3

Gut-transcriptome: A small (~3 mm^3) sample of the foregut epithelium will be collected during the participants routine upper endoscopy, performed in advance of bariatric surgery. The procedure will only be performed when an endoscopy is clinically indicated. This will be collected via aid of the endoscope using standard techniques. A similar size sample of the foregut epithelium is collected as a matter of routine clinical practice. We will be collecting a second sample for research purposes during the same procedure. The collected sample will be used to examine the gut transcriptome. Permission will be sought from the participants to retain any remaining tissues or derived extract(s) post-analysis in a deidentified manner for future research activities, including potentially DNA analysis. Participants will be able to opt out of the retention of material and/or future DNA analysis without compromising their status in the trial. Surplus tissue/extracts will be discarded via standard clinical waste streams if permission is not granted.

The collection of foregut tissue by endoscopy will be performed by the bariatric surgeons at the Clearlake Campus. Tissue will be temporarily stored at the site within -80 °C freezers owned by Surgical Pathology. These will be regularly transferred by study personnel to the PI's freezers located in MRB 10.110.

OTHER:

EMR blood test results: Metabolic profiles are regularly examined in bariatric patients pre- and post-procedure. We will record the results of any metabolism associated test (e.g. hemaglobin A1c, blood glucose concentrations) that are performed at any point while SURGERY participants are enrolled in the study. These will be collected from the patients Electronic Medical Record.

Exit survey: On completion of their involvement in the study, participants will be provided with a survey to complete (**Appendix VIII**). This will be sent to them by e-mail, with the answers returned anonymously using REDCap. Completion of the survey will be voluntary, with questions focused on their experience as a participant in the study. The survey will also ask hypothetical questions about other experimental techniques that we plan to perform in future trials, and how likely they would have participated if the procedures were a component of the present study. This information will help inform future study designs.

Data Coding: Following enrollment, all subsequently collected data will be coded. After screening, a unique random alphanumerical code will be assigned to each potential participant, which will be used for the remainder of all data and sample gathering activities. The deidentification key will be kept by the PI in a locked filling cabinet in their office (2.250F, SHP). The deidentification key will be securely destroyed at the conclusion of the study.

A summary of the primary data and samples due to be collected throughout the study, along with details of their storage location, follows:

Data type	**Storage location of samples and identifiable data**	**Security**
Consent records and subject key	Patient consents will initially be stored at the League City clinic in the office of Ms. Chelsea Hoover RD, before being transferred to the PI's Office on the Galveston Campus (2.250F, SHP).	Locked filing cabinet accessible only to study personnel.

Electronic records containing identifiable data; Screening data; Adverse events	SharePoint (*)	Encrypted drives with access restricted to study personnel.
Case Report Forms	Non-identifiable; PI & Investigators' Offices. Copies will be digitized and stored on SharePoint/REDCap (*)	Coded; Encrypted drives with access restricted to study personnel.
Instrument data files	Non-identifiable; Various locations including CHPPRR Research Labs, SHP; PI's Labs.	Coded
Biological samples	PI's Lab (MRB 10.110).	Coded; Temperature logs
Exit Survey	REDCap (*)	Coded; Encrypted drives with access restricted to study personnel.

(*) SharePoint storage will be within the Bariatric & Metabolic Research dedicated UTMB space accessible only to study investigators. SharePoint data is automatically encrypted using industry standard AES 256-bit keys by Microsoft's cloud service (see https://learn.microsoft.com/en-us/compliance/assurance/assurance-encryption-for-microsoft-365-services).

A flowchart detailing the storage location of data and samples, and how they will be transferred between locations is detailed in **Appendix IX,** and described in the table below**.**

Sample type	**Collection site**	**Storage conditions (*)**	**Incidental storage location**	**Permanent storage location**	**Transport between sites**
Foregut tissue	OR, UTMB Clearlake	Initial storage at CLC: -**18 °C** Permanent storage at Galveston: **-80 °C**	2.110 Laboratory Services, UTMB Clear Lake MRB 10.110, UTMB Galveston	RB6 2.230Q, UTMB Galveston	On dry ice, either by: UTMB Courier Services or the Investigators

(*) during storage, the following conditions will be considered acceptable:

-18 °C storage:	<8 hours	-10 °C to -18 °C
	No limit	-18 °C to -90 °C
-80 °C storage:	< 1 hour	-20 °C to -35 °C
	<72 hours	-35 °C to -60 °C
	No limit	-60 °C to -90 °C

Access to rooms housing freezers containing study specimens will be restricted to authorized users. The Investigators will monitor and maintain a log of the temperature status of the freezers housed in their laboratory (MRB 10.110). These freezers will be connected to a remote dialing service to alert Investigators in the event of freezer failure. Laboratory Services at Clear Lake Campus and the UTMB's Assay Development Service Division Core Lab, will oversee the monitoring and upkeep of their own facilities and will notify the Investigators of any issues with maintaining samples under the listed conditions.

Incidental storage of coded samples and data may occur outside of the above locations to permit transport between collection sites, to safe-guard samples in the event of freezer failure, or when being analyzed by UTMB Core Labs. When this occurs, the data/samples will be secured using the same level of security as outlined above.

At the conclusion of the trial, a database of the collected data will be created that excludes dates (e.g. visit dates and birthdates), except for the year, and the key linking the participant code to the individual will be securely destroyed. The final data and sample set will comply with the US Dept. of Health and Human Services' Safe Harbor method for the de-identification of data. Consent records will be retained in compliance with record retention requirements.

The primary data may be transferred to a secondary form (e.g. Excel and statistical software files, manuscript figures, ClinicalTrials.gov data deposit) and stored outside of the above locations. When this occurs, the data will not include any readily identifiable information.

Handling Missing Data: As is typical in most human intervention studies, there are occasions when it may not be possible to perform a procedure, collect a specimen, or record a data point (e.g. insufficient blood sample, equipment malfunction, or participant fails to follow instructions). When this occurs, a note will be made in the participant's case report form highlighting the cause for the missing data/inability to perform a procedure.

If an individual of the SURGERY Group fails to undergo bariatric surgery for any cause, they will be withdrawn, with their data retained. An individual withdrawn prior to post-surgical follow-up will not count towards the cap on the number of patients recruited. Participants will be replaced on a 1:1 basis.

6.0 Study Product Description

Study is not a randomized controlled drug trial.

7.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Below follows a breakdown of potential foreseen risks of the various study procedures. If a procedure is not listed, it is not considered to present a risk to either the volunteers or others.

Blood Sampling. The risks of phlebotomy include pain and infection if aseptic procedures are not used. Repeated blood draws or excessive sampling volume also increases the risk of anemia. We will limit blood collection, up to 10 mL of blood at a single blood draw. Trained personnel will use strict aseptic technique for all blood draws.

Biopsy of the foregut epithelium: The collection of biopsy material from the foregut during an upper endoscopy is a routine minimally invasive procedure performed when warranted prior to bariatric surgery. In addition to the standard sample taken as routine care, we will collect an additional ~3 mm^3 sample for our research purposes. Bleeding or a tear in the mucus membrane of the digestive tract are possible risks, occurring in less than 1% of all cases.

Loss of confidentiality: Every effort will be taken to maintain participant confidentiality. Data will be coded at source, with access to the deidentification key, consent forms, and screening data secured in a lockable filling cabinet, and access restricted to key staff. At study closeout, the deidentification key will be destroyed and the HHS Safe Harbor principles employed to prevent future reidentification of study data. Despite these mitigation strategies and in common with all human trials, a risk for the loss of confidentiality remains.

Adverse events following bariatric surgery: Between experimental visits, the SURGERY Group will undergo elective weight loss surgery using standard protocols. The decision to undergo bariatric surgery or what type

of surgery is offered (e.g. gastric sleeve or bypass), will be decided upon by the patient and their physician independent of the research study. Laparoscopic robotic assisted bariatric surgery is associated with the following risks: conversion to open procedure; failure of device requiring additional surgical procedure; obstructive symptoms requiring additional surgical procedure; development of gallstones; development of metabolic and vitamin disorders; suture line leak with abscess or fistula formation; failure of wound to heal or wound dehiscence; and gastroesophageal reflux disease. General risks of surgery performed under general anesthesia also apply: infection; blood clots in veins, lungs or other organs; hemorrhage; allergic reactions; poor wound healing; and death.

Process for the reporting of adverse events or unanticipated problems:

ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for "serious adverse events" will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include MD, PA, Nurse Practitioner, DO, or DDS), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the patient is screened will be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it will be recorded as an AE.

All AEs will be graded for severity and relationship to study interventions.

Severity of Event: All AEs will be assessed by the clinician using the following guidelines to quantify intensity.

- Mild: events require minimal or no treatment and do not interfere with the patient's daily activities.
- Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Life threatening: any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

Changes in the severity of the AE will be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent will require documentation of onset and duration of each episode.

Relationship to Study Products: The clinician's assessment of an AE's relationship to the test article is a part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported. All AEs will have their relationship to study product assessed using the terms: associated or not associated. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines will be used.

- Associated – The event is temporally related to the administration of the study product and no other etiology explains the event.

- Not Associated – The event is temporally independent of study product and/or the event appears to be explained by another etiology.

Serious Adverse Event (SAE): An SAE is defined as an AE that meets one of the following conditions:

- Death during the period of protocol defined surveillance
- Life-threatening event (defined as a subject at immediate risk of death at the time of the event)
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All SAEs will be:
- recorded on the appropriate SAE CRF
- followed through resolution by a study clinician
- reviewed and evaluated by a study clinician

Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

At time of medical screening, abnormal test results, defined as being outside of normal established reference ranges, or if already noted as abnormal in the individual's medical record, a worsening of their condition, will be reported to the individual and their Primary Care Physician.

Following enrollment, no laboratory test of clinical prognostic value are due to be collected as a component of the research trial. Abnormal clinical findings may occur: i) during routine clinical interactions between the participant with the bariatric surgery team and support staff post-surgery, ii) self-reported by the participant to the investigatory staff, or iii) following notification via EPIC. When this occurs, the Study Clinician will be consulted and the reporting procedure outlined below followed.

Reporting Procedures

Abnormal laboratory values: Abnormal laboratory values, identified at the time of medical screening, will be reported to the Study Clinician and within 1 week of coming to the attention of study personnel, the PI or Study Clinician will notify the individual and their Primary Care Physician of the abnormal findings. This will not constitute an adverse event as no study procedures will have been performed at the screening stage.

Abnormal clinical findings: Following notification/identification by a member of the Investigatory team, the PI will be notified and the Study Clinician consulted within 5 working days, except in the case of serious adverse events, where same day notification will be attempted.

Any AE considered serious by the PI/Study Clinician, or which meets the aforementioned criteria will be submitted to the IRB in accordance with IRB policies and procedures, and as described below.

The PI will complete the Adverse Event Form (**Appendix X**) in consultation with the Study Clinician within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form and sent to the IRB within 2 days of PI's/study staff's awareness.
- Serious adverse events other than death and immediately life-threatening events, that are related or possibly related to the study, will be reported within 10 days of PI's/study staff's awareness.
- All other SAE's that occur will be reported at Continuing Review.

All SAEs will be followed until satisfactory resolution or until the Study Clinician deems the event to be chronic or the patient to be stable.

8.0 Study Withdrawal/Discontinuation

Reasons for Withdrawal

A study subject will be discontinued from participation in the study if any of the following occur:

- SURGERY Group: The individual does not ultimately undergo bariatric surgery at UTMB.
- The participant fails any component of the pre-surgical clearance for bariatric surgery.
- Unacceptable toxicity or adverse event (AE)
- Unacceptable laboratory abnormalities
- Intercurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject in the opinion of the treating investigator
- Development of any exclusion criteria before the endoscopy procedure has been completed. If an upper endoscopy is not required or it has already been completed, the presence of AE will not be grounds for withdrawal.
- Subject withdrawals consent to continue in the research for any reason
- Persistent failure by the subject to follow the instructions of the Investigators.

Handling of Withdrawals

All participants who are withdrawn, whether voluntarily or for the defined reasons outlined above, will be contacted and asked to complete the standard end of study questionnaire (**Appendix VIII**). If participants have withdrawn due to an adverse event, the participant will be contacted by one of the Investigatory team and an adverse event record created for review by the Study Clinician. If the adverse event is not transient and determined by the Study Clinician to be potentially due to study interventions, regular contact will be made by the Investigatory team to track changes in the subject's condition and the adverse record updated and reviewed by the Study Clinician. The frequency of follow-up will be decided by the Study Clinician and continue until either i) the condition is fully resolved; ii) no change in the subject's condition is expected to occur; or iii) the participant fails to respond to attempts at contact.

Participants of the SURGERY Group who fail to undergo bariatric surgery for any cause will be replaced on a 1:1 basis. Data from all withdrawn participants will be retained.

Termination of Study

The study will be prematurely terminated if any of the following criteria occur:

- An unexpected loss of study funding.
- On instruction from the IRB.
- Persistent adverse events that are deemed due to study procedures that cannot be overcome by a reasonable modification to the study protocol.

9.0 Statistical Considerations

The trial is a **pilot** and mechanistic in nature – it does not involve the assignment of treatments. Furthermore, the study is to take place solely at UTMB. Study data will be analyzed on conclusion of the trial using the Intention-To-Treat principle.

Participant characteristics are as described in section 3.0 above. The following table outlines the outcome measures by objective, the comparisons to be made, and the statistical tests that we will employ.

Outcome Measure		Data type	Comparison	Statistical test
Specific Aim 2: Examine the association between a patient's gut transcriptome on energy intake, muscle function, and weight loss following bariatric surgery.				
1°	Gut transcriptome	Continuous; large data	SURGERY: i) Baseline	DESeq2 as described in (13)
2°	Energy Intake	Continuous	SURGERY: i) Baseline ii) Post-surgery iii) Long-term follow-up	One-way ANOVA - repeated measures
	Hand grip strength			
	Body weight			
	Fat mass			

Continuous data will be tested for normality using the Shapiro-Wilk test and log transformed if required. When a significant main effect is observed ($P<0.05$), a Fisher's LSD post hoc test will be applied to locate significant differences between groups. When performing repeated measures ANOVA, if missing data is encountered, we will utilize a compound symmetry covariance matrix, fitted using restricted maximum likelihood (REML). Data analysis will be performed using Prism (GraphPad) and R. Significance will be accepted when $P<0.05$.

Objective: We will recruit 100 SURGERY patients, allowing us to interrogate the association between the patient's gut transcriptome with the degree of weight loss achieved post-procedure. As our first foray into this area of research, and in keeping with the pilot nature of the work, we do not have preliminary data upon which to perform sample size calculations. Notably, the numbers to be recruited are comparable with similar studies aimed at identifying genetic drivers of weight loss in other populations (15-17), providing confidence that our recruitment plans are appropriate. Regardless, the data obtained will provide us the necessary information from which to perform power calculations for future larger confirmatory trials.

Safety Oversight: Data safety monitoring will be performed by the PI, with support from the investigatory team. The investigatory team will meet regularly (minimum of once a month) while there are active participants in the study. At these meetings, adverse events and their attribution to study interventions will be discussed. Given that we are relying on well-established techniques, we don't anticipate any serious events because of the study protocol. Nonetheless, the occurrence of adverse events will be kept under constant review, and the study procedures refined if a causal link between study interventions and adverse events is established (occurrence >20%).

10.0 Ethical Considerations and Privacy/Confidentiality Issues

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

The investigator must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate independent ethics committee (IEC) or IRB registered with the OHRP. Any amendments to the protocol or consent materials must also be approved before they are placed into use. In the United States and in other countries, only institutions holding a current US Federal wide Assurance issued by OHRP may participate.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of participating in this study will be provided to the subjects. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting study interventions. Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Privacy/Confidentiality Issues

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Principal investigator.

Individuals authorized to view study records will be identified to the study subject on the informed consent but may include a study monitor or other authorized representatives of the sponsor or funding agency or federal or local agencies that regulate research including representatives from the Food and Drug Administration, Office of Human Research Protections, or the Institutional Review Board. Study records may also be made available for internal compliance reviews and quality assurance representatives. These individuals may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

In accordance with the Food and Drug Administration Amendment Act of 2007 (FDAAA) and The International Committee of Medical Journal Editors (ICMJE) member journals trials-registration policy as a condition for publication, this study will be registered in the public trials registry ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Results will be published to clinicalTrial.gov when available but will not identify individual subjects. Similarly, the Investigators intend to publish their findings in peer-reviewed scientific journals, where data will be presented in a manner that prevents the identification of individuals.

11.0 Record Retention

The human participation phase of the trial is anticipated to last two years, with a further year of data analysis (3 years total). Research records generated during the life of the trial will be maintained in accordance with the current version of the Texas Health Records Table 17-III Record Retention Schedule, Human Subject Research Records and Documents. Currently, according to UTMB's official record with the State Library and Archives Commission, the institution requires indefinite retention of information generated during medical research and clinical trials that are not associated with extramural grants. To comply with this mandate, on conclusion of the trial, records will be retained by the PI in a locked filling cabinet under their control and/or in electronic password protected and encrypted files on UTMB's cloud storage. If the PI leaves the institution or the records become inactive, they will be submitted to UTMB's Office of Records Management Compliance for long-term storage.

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