Time-Restricted Eating and Cancer:
Clinical Outcomes, Mechanisms, and Moderators
NCT04722341

January 8, 2023

Jane C. Figueiredo, Ph.D.
Cedars-Sinai Cancer

Sarah-Jeanne Salvy, Ph.D.
Cedars-Sinai Cancer

Courtney Peterson, Ph.D.
University of Alabama at Birmingham

TABLE OF CONTENTS

PROTOCOL SUMMARY

Purpose and Knowledge to be Gained	• The purpose of this study is to test whether the timing of meals can improve treatment-related adverse events, influence tumor biology, and alter a person's mood and behaviors. • This work has the potential to understand the role of meal timing and alignment of circadian rhythm on toxicity burden, tumor regression, and ultimately provide evidence-based knowledge to influence the standard of care for cancer patients. Importantly, these findings may have broad oncologic implications, likely extending to other cancer disease sites and treatment paradigms.
Research Procedures	The primary research procedures are: • Randomization into one of two arms (TRE or control) • Medical chart abstraction • Blood draws • Continuous glucose monitoring (CGM) • Stool collection • Weight, height, heart rate, and blood pressure • Short weekly surveys (a few minutes per week) • Portable accelerometry sensor to measure physical activity • Questionnaires about pain, fatigue, sleep, mood, physical activity, food intake, quality of life, and social life • Exit interview (end of intervention)
Subject Population	• Any sex/gender of any ethnic/racial background • Age ≥ 18 years • Histologically confirmed rectal cancer stage II, III, or IV (only if definitive intent) per AJCC criteria • BMI ≥ 18.5 kg/m^2 • Plan to receive total neoadjuvant therapy (TNT) with 5-FU based regimen • Willing and able to adhere to the assessments, visit schedules, prohibitions, and restrictions
Duration	• The study includes three required study visits between enrollment and surgery (or the equivalent time frame). • The total study duration is up to 5 years.

GENERAL INFORMATION

CSMC Co-Investigators	Jun Gong, MD Katelyn M. Atkins, MD, PhD Karen Zaghiyan, MD Gillian Gresham, PhD Márcio Augusto Diniz, PhD Alix Sleight, PhD
Sponsor/Funder	National Institutes of Health/ National Cancer Institute
Collaborating Institutions Involved in the Research	University of Alabama at Birmingham: Courtney Peterson, PhD Drew Gunnells, MD Robert Hollis, MD

1.0 BACKGROUND, RATIONALE

Combining fasting with chemotherapy is known to cause complete tumor regression and long-term survival in animal models. According to the Differential Stress Sensitization (DSS) theory, acute fasting sensitizes tumor cells to the cytotoxic effects of chemotherapy and radiation, while protecting healthy cells by increasing stress resistance. These effects are believed to be largely mediated via the Insulin-like Growth Factor (IGF-1) pathway. However, extended fasting can be challenging for patients and poses undue health risks. A number of alternative intermittent fasting regimens have been proposed to overcome the challenges of prolonged caloric restriction. One promising approach is time-restricted eating (TRE), which involves eating within a period of 10 hours or less, followed by fasting for at least 14 hours daily. TRE does not involve extended caloric restriction, and because of its simplicity, it may be more sustainable than other fasting regimens. TRE improves several cardiometabolic endpoints independent of calorie restriction in both animals and humans, including insulin sensitivity, blood pressure, fat oxidation, and hunger. Our team's pilot and feasibility trials suggest that TRE may also have anti-cancer effects: it decreases IGF-1 levels, reduces oxidative stress, upregulates antioxidant defenses, and enhances autophagy. Moreover, our data suggest TRE is sustainable, as participants were adherent 6.0 ± 0.8 days/week over a 14-week period. These findings lead to the following provocative question: Can TRE reduce treatment-related toxicity, induce tumor regression, and improve both patient-reported and clinical outcomes? We propose to conduct the largest randomized controlled trial of any form of intermittent fasting in patients undergoing cancer treatment. We focus on patients with localized rectal cancer because it is one of the few treatment paradigms in which tumor characteristics can be measured before and after chemoradiation therapy.

2.0 STUDY OBJECTIVES

This research will answer three key questions:

(1) Can TRE improve clinical outcomes, including treatment toxicity, patient-reported outcomes, and increase the chances of tumor regression (i.e., help shrink the tumor)?

(2) Do the underlying molecular mechanisms support the Differential Stress Sensitization theory?

(3) How does TRE affect mood, social functioning and lifestyle behaviors to moderate patient outcomes?

As the largest randomized controlled trial of TRE in cancer patients, we expect this trial will greatly influence clinical practice

3.0 STUDY POPULATION

3.1 SELECTION OF THE STUDY POPULATION

The study population includes adults diagnosed with localized rectal cancer (ICD-10 C20, stage II, III, or IV [if definitive intent]) who receive neoadjuvant treatment as part of their clinical care. All patients are treated at Cedars-Sinai Medical Center, UAB or referring sites.

3.2 INCLUSION CRITERIA

- Any sex/gender of any ethnic/racial background
- Age ≥ 18 years
- Histologically confirmed rectal cancer stage II, III, or IV (if curative) per AJCC criteria
- BMI ≥ 18.5 kg/m^2
- Will receive total neoadjuvant therapy (TNT) with 5-FU based regimen
- Willing and able to adhere to the assessments, visit schedules, prohibitions, and restrictions

3.3 EXCLUSION CRITERIA

Applicants will not be eligible to participate if they meet any of the following criteria:

- History of cytotoxic chemotherapy ⩽12 months prior to rectal cancer diagnosis
- Allergic reaction to any of the treatment agents
- Any prior pelvic radiotherapy
- Currently active second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ
- History of GI perforation ⩽12 months prior to enrollment
- History of predisposing colonic or small bowel disorders with severe or rapidly worsening symptoms (not related to current cancer symptoms)
- Receiving any parenteral nutrition or enteral (tube) feeding or using similar nutritional supplement during the study period
- History of uncontrolled CHF defined as NYHA Class III or greater
- Pre-existing grade ⩾3 neuropathy

- Currently participating in or has participated in a study of an investigational agent or investigational device ⩽4 weeks of the first dose of treatment
- Pregnant or breastfeeding
- Currently perform overnight shift work more than one day/week on average
- Strictly adhering to a <10-hour eating window on most days
- Known psychiatric or substance abuse disorders that would interfere with adhering to the requirements of the trial

3.4 SUBJECT SCREENING AND ENROLLMENT

All screening and identification work will be done via study staff using approved methods for patient contact and recruitment including EHR, Deep6, electronic communications and/or telephone.

3.5 SUBJECT RECRUITMENT

Participants will be recruited from Cedars-Sinai Medical Center (CSMC), University of Alabama's O'Neal Comprehensive Cancer Center (UAB), and from referring sites using two different approaches:

Clinic. At CSMC, UAB or referring sites, the study oncologists (co-Is) or referring physicians/surgeons will introduce the study to their patients and connect interested patients with study staff. If the patient expresses interest in participating, staff will carefully review the full consent form with the patient in person, via phone, or via IRB-approved electronic communication platforms (such as Zoom) and answer the patient's questions about the study. Participants will be allowed to electronically sign consent forms online using DocuSign, REDCap's e-consent tool, or printed forms in-person.

Medical Records. At CSMC and UAB, research staff will review medical records of potential participants in order to identify patients who may be eligible. Deep6 (or the equivalent) will also be used for rapid searches of electronic medical records to identify patients with specified criteria to recruit into studies. In other instances, patients will be contacted by the research team only after the treating physician/surgeon has broached the topic of participation in a research study and received confirmation that the patient is interested in learning more about the trial. The treating physician/surgeon will be provided with the study consent form and any other information summarizing study participation that has been approved for use with potential participants. After the initial recruitment process, a follow-up phone call will be made by a trained recruiter to answer questions and solicit participation if study consent was not received by treating physician or study coordinator at in-person visit.

4.0 STUDY DESIGN AND METHODS

This study is a prospective, single-blinded, two-parallel-arm, randomized controlled superiority trial comparing time- restricted eating (TRE) to a control eating schedule (Control). We will enroll 300 economically, ethnically, and racially diverse women and men newly diagnosed with

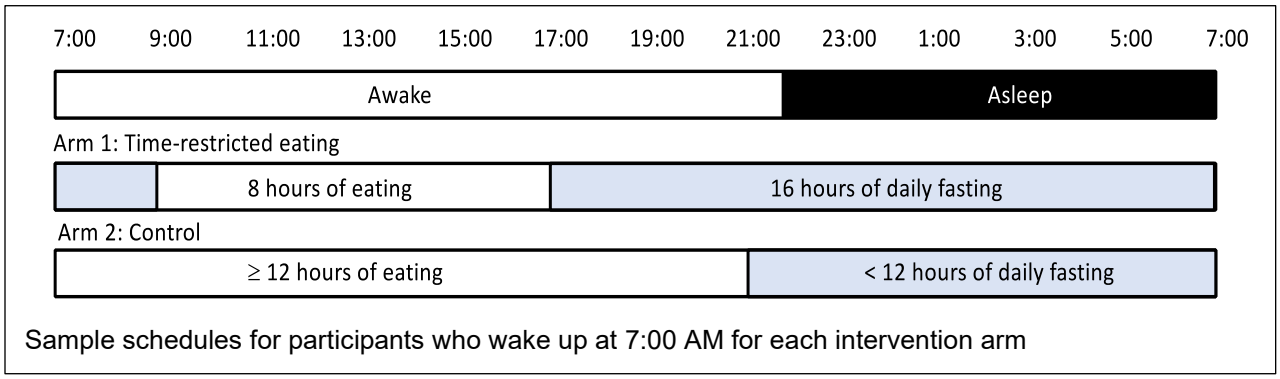
rectal cancer (stage II, III, or IV [if definitive intent]) and who are undergoing TNT. Patients will be enrolled from Cedars-Sinai Medical Center (Los Angeles, CA), UAB's O'Neal Comprehensive Cancer Center (Birmingham, AL) or referring sites. Randomization will be blocked in permuted blocks of random size and stratified by radiation sequence (before vs. after chemo), T stage (T4 vs. T3 or less), sex (male vs. female), and site (CSMC vs. UAB). The randomization list will be completed by the biostatistician and uploaded in REDCap. Behavioral counselors will randomize eligible participants using the REDCap randomization tool.

Providers and outcome assessors will be blinded, except for S.J.S., counselors, and dietitians who cannot be blinded as they are providing counseling/safety monitoring for the intervention. Participants will also not be blinded to the intervention but will not be aware of which arm is expected to have a better outcome.

Intervention Arms. All participants will receive the standard of cancer care from their respective healthcare providers. We will aim to enroll most participants shortly before or at the time of starting treatment, though patients may enroll after starting treatment as long as they have not complete a majority of their planned oncologic treatment. Participants will be randomized to one of two groups:

(1) Time-restricted eating (TRE): a consistent daily ≤8-hour eating period, starting within 2.5 hours after waking up, or
(2) Control group: ⩾12-hour eating period each day.

Participants will be instructed to follow their assigned meal-timing schedule ⩾6 days/week every week. To account for inter-individual differences in sleep and circadian rhythms, we timed the TRE schedules relative to sleep time (not clock time), which is a reasonable proxy for circadian time. The control group was designed to mimic typical eating habits in the U.S., as data from NHANES suggest that the median American eats over a ~12-hour period each day.[1] Aside from these general prescriptions, no set number of snacks, meals, or calories will be prescribed. Instead, we measure how TRE affects self-reported meal-times, meal frequency, and food intake through a combination of daily adherence surveys and 3-day food records.



Sample schedules for participants who wake up at 7:00 AM for each intervention arm

Standard of Care. All participants will receive the standard of care at CSMC, UAB and referring sites. Standard of care is provided by registered dietitians with master's degrees and

board-certification in oncology nutrition. Every new patient starting chemotherapy in the infusion center will meet with a dietitian for a nutrition consultation. Patients can also be referred to a dietitian by a physician if warranted by the malnutrition screening tool (MST) and the Wellbeing Screening Tool. Nutrition consults include a nutrition assessment, development of individualized nutrition care plans, and nutrition counseling and/or education. Dietary recommendations and goal setting are based on cancer diagnosis, medical history, treatment plan, laboratory values, nutrition-focused physical exams, and the patient's personal dietary preferences. Follow-up appointments are scheduled based on clinical need and nutrition risk (high, moderate, low) as determined by the dietitian, as well as patient preference. If there are any differences in standard of care practices as described here at the referring sites, then local site practices will be followed. For this trial, all participants will be evaluated by a dietitian at enrollment (45 minutes of one-on-one diet counseling) and re-evaluated monthly to monitor participants' weight, blood pressure, and adverse events. Participants may receive more frequent dietary counseling, if recommended by the MPIs and/or physicians.

Intervention Dosage and Fidelity. Intervention fidelity encompasses integrity (interventions are implemented according to established procedures) and differentiation (interventions are distinct from one another).[37] We will implement the following strategies and safeguards to preserve intervention integrity and differentiation: (1) Comprehensive assessment of the standard of care avoids content overlap between intervention arms, (2) asking participants to record the time they started and finished eating every day, and (3) frequent contacts with participants to review adherence to meal timing and to problem-solve issues and challenges encountered. In our experience, participants feel comfortable reporting whether they followed the assigned meal schedule and report challenges precluding them from adhering to meal timing. If a participant adheres to meal timing protocol <4 days/week, a follow-up call or videoconference will be scheduled to address challenges and to counsel participants. Each participant will meet monthly with the clinical dietitian to review his or her dietary intake and to address concerns.

Behavioral Counseling. All participants will meet with a behavioral counselor who is also a dietitian (trained and supervised by S.J.S.) on a frequent basis to promote adherence. During the first one-hour counseling session, the dietitian will explain their assigned study arm and answer questions. Thereafter, participants will meet with their counselor weekly for the first month, and monthly therafter, unless additional support is needed. Follow-up counseling sessions will typically be short (~15-30 minutes).

Adherence. Participants in both groups will be instructed to follow their assigned eating schedule at least 6 days/week every week. Participants will be asked to self-report their adherence using a weekly survey, which asks participants to record the time they start and finish eating each day and to document any reasons for non-adherence. Participants may complete the survey via REDCap, by text message, or on paper, as preferred. Days with missing data will be counted as non-adherent. If a participant adheres to their assigned meal timing protocol <4 days/week, a follow-up call or videoconference will be scheduled to address challenges and to help problem solve barriers to adherence.

Reducing Attrition. We will use strategies that we have found effective for retention, such as: (1) providing all participants with a $50 gift card at 3 data collection timepoints, with all incentives paid after assessments have been completed; (2) ensuring regular contacts (texts or calls) with all participants to maintain engagement and foster open communication; (3) acknowledging birthdays and milestones; (4) providing reminder phone calls before assessments; and (5) seeking contact information of relatives or friends to be able to reach participants. In addition, Internet-based data collection will allow us to monitor patient compliance in real-time and provide phone, text, and email reminders for timely completion as needed

Clinical and Outcomes Assessment:

Medical Chart Abstraction. Several clinical variables will be extracted from medical records, including demographics, anthropometrics, medical history, vital signs, tumor markers (e.g., CEA) the date of diagnosis, disease stage (TNM staging), MSI status, surgical treatment (e.g., dates and type), chemotherapy (e.g., agents, dose, dates and number of infusions), and radiation therapy (e.g., dates, number of treatments, and dose). Treatment-related toxicities will be also extracted from medical records. We will use the standard approach to AE reporting in cancer trials, which is the Common Terminology Criteria for Adverse Events (CTCAE), maintained by the US National Cancer Institute (NCI).

Testing Visits. Testing visits will be used primarily to collect blood samples, anthropometrics, and vital signs and to administer questionnaires, continuous glucose monitors, and accelerometers. In-person testing visits will be conducted at three timepoints: baseline, in the middle of the intervention, and post-intervention. The baseline visit will be conducted as soon as possible after consenting each patient. The post-intervention visit will be conducted in the couple weeks prior to surgery or when surgery would have been scheduled. Each testing visit will be conducted after a 8-hour or longer fast. To reduce participant burden, participants may choose to complete their questionnaires at home, rather than during the in-person testing visit.

Co-Primary Endpoints. The co-primary endpoints will be the pathological Complete Response (pCR) rate and treatment-related toxicity. pCR will be defined as an absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected rectal specimen and all sampled regional lymph nodes. It will be treated as a binary variable. The Patient Reported Outcome-Common Terminology Criteria for Adverse Events (PRO-CTCAE v.5) measurement system will be used to measure treatment-related toxicities. We will administer the PRO-CTCAE on a weekly basis throughout the intervention and calculate the average over all items for each time point. Surveys will be timed relative to the start of each oncologic treatment segment.

Secondary Endpoints. Secondary endpoints include the Clinical Complete Response (cCR), tumor volume, objective response rate (ORR), neoadjuvant rectal (NAR) score, provider-reported adverse events, health-related quality of life, and other clinical outcomes. Descriptions of the secondary endpoints are provided below.

- **Clinical Complete Response (cCR).** A cCR will be defined as the clinical absence of residual disease on physical examination, endoscopic examination, and/or repeat MRI imaging following completion of total neoadjuvant treatment.
- **Tumor Volume.** Standard of care CT and MRI images will be obtained at the time of diagnosis for staging. A repeat standard of care MRI imaging may be obtained prior to surgery to assess response to neoadjuvant therapy and to guide clinical and surgical management. We will obtain routine clinical restaging scans from participants and use them to estimate changes in tumor volume between the two time points. We may also use the scans to explore changes in body composition.
- **Objective Response Rate (ORR).** We will also assess the ORR, which is defined as the percentage of people who have a partial response (defined as a decrease in tumor volume) or a complete response to treatment between enrollment and surgery.
- **Neoadjuvant Rectal (NAR) Score.** The NAR score is a validated surrogate endpoint for oncologic outcomes used in rectal cancer clinical trials. It takes as input the pathologic nodal status and the clinical and pathologic T-stage.
- **Secondary Measures of Toxicity.** As secondary measures of toxicity, we will collect provider-reported adverse event data. We will analyze the incidence of grade 3-4 toxicities and calculate the aggregated Toxicity Index (TI). The TI accounts for the frequency and cumulative burden of all toxicities during the treatment period.
- **Health-Related Quality of Life.** We will use the widely-used and validated European Organization for Research and Treatment of Cancer Quality of Life (QOL) core questionnaire C30 (EORTC QLQ-C30) and the colorectal-cancer specific questionnaire (EORTC CR29). For this study, we focus on highly prevalent rectal cancer treatment-related symptoms, including fatigue, insomnia, pain and bowel-related items (stool frequency, flatulence, and fecal incontinence).
- **Other Clinical Outcomes.** We will also attempt to collect follow-up data on progression-free survival (PFS), relapse-free survival (RFS), and overall survival (OS).

Additional Endpoints. Several additional endpoints are described below.

Questionnaires. Participants will be asked to complete standard/validated questionnaires using web-based or paper-based forms. Questionnaires and recalls will be administered by experienced study coordinators (bilingual: English/Spanish). Specific questionnaires will include the General Physical Activity Questionnaire (GPAQ), Munich Chronotype Questionnaire (MCTQ), the Pittsburgh Sleep Quality Index (PSQI), the Appetite Questionnaire (AQ; includes a couple extra visual analogue scale questionnaires), the Dutch Eating Behaviors Questionnaire (DEBQ), Satisfaction with Participation in Discretionary Social Activities Questionnaires, UCLA Loneliness Scale (short version), two cancer-related quality of life questionnaires (EORTC QLQCR29 and EORTC QLQ30), the Patient Health Questionnaire-8 (PHQ-8), and NIH PROMIS scales relating to physical function, fatigue, and emotional distress/anxiety.

Anthropometrics. Participants' height will be measured at baseline or extracted from the medical record (if measurement by research staff is not possible). Weight will be measured using an electronic scale according to standard procedures during clinical care. Blood pressure and

heart rate will also be measured at each testing visit according to standard procedures during clinical care.

Biospecimen Collection and Analyses. Blood specimens will be collected at three time points: baseline, 3 months, and pre-surgery, with an optional fourth collection in between treatment segments (radiation vs. long-course chemo). Participants must fast at least 8 hours prior to collection. Blood specimens will be used to measure IGF-1 and its binding proteins—IGFBP-1 and IGFBP-3. Samples will be measured in duplicate using ELISAs from American Laboratory Products Company (ALPCO; Salem, NH, USA). We will also measure fasting glucose, insulin, and lipid levels, as well as complete blood counts (CBCs). Glucose will be measured on a DXC600 instrument (Beckman Coulter; Brea, CA, USA) using standard reagents, while insulin will be measured using chemiluminescent immunoassays on an Immulite 2000 instrument (Siemens Corporation; Washington, DC). We will also collect peripheral blood mononuclear cells (PBMCs) to represent healthy cells. PBMCs will be obtained as follows. In brief, PBMCs will be obtained by collecting whole blood and transferring it into Leucosep tubes containing Lymphoprep reagent (StemCell Technologies Inc.; Cambridge, MA), following the manufacturer's instructions. The resultant solution will be centrifuged at 1000-1200 g for 12 minutes with the brake on. The mononucleocyte layer will be transferred into a new Leucosep tube and centrifuged at 400 g for 6 minutes. Most of the supernatant will be discarded, and the white pellet will be resuspended in the remaining 1-2 mL of supernatant. After determining cell density, the solution will be centrifuged again at 400 for six minutes, and the remaining supernatant will be discarded. The pellet will then be resuspended using Invitrogen™ RNAlater™ (Life Technologies Corporation; Carlsbad, CA) and frozen at -80ºC for future analyses. PBMCs will be used to measure indicators of stress resistance, such as total antioxidant capacity (catalog #ab65329; Abcam plc; Cambridge, MA). Lastly, FFPE slides with normal/rectal tumor tissue will be obtained as part of the standard of care and will be obtained by request from each site's Department of Pathology. We will obtain slides of FFPE normal/tumor tissue from the diagnostic biopsy and at resection, whenever possible.

Protein Expression. To test the differential stress resistance (DSR) theory, we will measure markers representing cell growth and death dynamics and stress resistance, including Ki67 (cell proliferation), caspase 3 (apoptosis), LC3-I/LC3-II (autophagy), and γ-H2AX (DNA damage). Protein expression will be measured in FFPE tumor and adjacent normal tissue using Nanostring's GeoMx technology (Nanostring Technologies, Inc.; Seattle, WA). Nanostring's technology involves multiplex antibody cocktails that have been barcoded with unique synthetic DNA oligonucleotides that are recognized by a unique reporter probe conjugated to a fluorescent barcode. We will use monoclonal, knockout-validated antibodies from Abcam (Abcam plc; Cambridge, MA). Samples will undergo cycles of incubation and hybridization with the fluorescent tags and then will be loaded an nCounter instrument to quantify expression levels. We will use NanoString's nSolver software to quantify expression levels, using the geometric mean of selected housekeeping proteins.

Continuous glucose monitors (CGMs). Abbott FreeStyle Libre Pro CGMs will be used at baseline and around the time of surgery (post-intervention) to measure blood sugar levels. Continuous glucose monitoring tracks glucose levels in interstitial fluid at regular and frequent intervals to generate dynamic information on mean 24-hour levels and glycemic excursions/variability.

Stool Collection (Optional). At baseline and before surgery, patients will be asked if they would be willing to take home a stool collection kit. If they are willing and able, the patients will then be asked to provide a stool sample from home prior to surgery date. If we cannot collect stools using these methods, we will try to collect remnant stool leftover from clinical procedures. All materials for the stool sample collections (including gloves, stool collection containers, written instructions, a return mailer, and a short questionnaire) will be provided by mail or at the initial office visit. Stool samples can also be collected via a digital rectal exam. Stool samples collected at home will be placed in the provided mailing containers and frozen overnight at 0°C. Then the frozen sample will be shipped to Cedars in the pre-paid self-addressed mailer that we will provide. Upon arrival at Cedars, the stool sample will be frozen at -80°C until processing.

Dietary Intake. Dietary intake will be assessed using three-day food records at baseline, the intermediate time point, and prior to surgery. To analyze participants' food intake, we will use the Nutrition Data System for Research software (NDSR; Nutrition Coordinating Center, University of Minnesota). We will assess changes in total energy intake, macronutrient composition, and the Healthy Eating Index (HEI 2015), as well as changes in added sugar, fruits, and vegetables, solid fats, alcoholic beverages, and sodium between groups.

Physical Activity. Wrist actigraphy is a non-intrusive, objective measure of sleep and physical activity. Each participant will be instructed to continuously wear an Actigraph (Pensacola, FL) on the non-dominant wrist for a week at baseline and around the time of surgery. The actigraph uses a piezoelectric accelerometer to measure the degree and intensity of motion, sampling every second. Physical activity will be operationalized as the mean metabolic equivalent units (METs) per hour and percent of time spent in sedentary, light, moderate, and vigorous activity, as assessed by the Friedson (2011) algorithms. To objectively measure sleep, we will use an open-source and validated set of algorithms to assess sleep and activity outcomes (GGIR package, R-software).

Exit Interview. A study team member with expertise in qualitative methodology will conduct semi-structured qualitative interviews with each participant at the conclusion of the intervention. The goal of these interviews will be to present open-ended questions about how participants experienced their assigned eating schedules in the context of cancer treatment, symptoms, and side effects, and in the context of their roles, values, and routines. Participants will also be asked to discuss challenges they faced (if any) with habit changes needed to adhere to a new eating schedule, as well as any positive or negative outcomes that they felt stemmed from this new eating schedule. Interviews will be audio-recorded and transcribed verbatim. Dedoose™ software will be used for analysis of qualitative data. Data analysis will be informed by a social constructivist, interpretive framework consistent with grounded theory and interpretive. Independent coding of transcripts will be completed by two researchers trained in qualitative methodology, and a codebook will be developed using *in vivo* codes that emerged during interviews as well as *a priori* codes originating from background concepts that inform the overall research problem (e.g., "social components of eating"). Discrepancies in coding will be resolved by a third member of the study team with qualitative expertise. Themes uncovered by this qualitative investigation may inform the interpretation of acceptability and feasibility data.

.

Schedule of Procedures

	METHODOLOGY		Initial Visit	Transition Visit (Optional)	3-month Visit	Before Surgery Visit
Adherence to meal schedule	• Eating schedule daily log completed by all participants (TRE and control) • Weekly/monthly contact with staff to problem-solve challenges with mela schedule adherence					
Demographic and medical history	• Baseline questionnaires and medical chart reviews					
Blood draws	• Hospital phlebotomist/RN at clinical sites					
Weight, Height, Heart Rate, Blood Pressure and Waist circumference	• Hospital phlebotomist/RN at clinical sites; trained study staff					
Exit interview	• Semi-structured interview					
Treatment tolerability/toxicity	Assessed adverse events	CTCAE v. 5.0				
	Patient-reported adverse events	PRO-CTCAE				
Patient-reported HR QOL	Health related Quality of Life	EORTC QLQ30 and EORTC QLQCR 29				
Continuous glucose monitoring	Abbott FreeStyle Libre Pro					
Stool collection (optional)	• In-home or clinic collection kit					
Psychosocial functioning	• Questionnaires					
Mood	• NIH Patient-Reported Outcomes Measurements Information System (PROMIS©) anxiety and depression short forms					
Sleep	• Questionnaires: MCTQ, PSQI • Objective accelerometry using wrist-worn actigraphy					
Dietary intake	• 3-day food records					
Daily physical activity/movement	• Objective accelerometry using wrist-worn actigraphy					
Tissue collection	• Biopsy and surgeries as part of standard of care					

5.0 DATA COLLECTION AND MANAGEMENT

5.1 DATA PROCUREMENT

- Data will be collected by the investigators and study staff from the EHR, with manual procurement from each participant's electronic chart as needed, from the questionnaires, and from assay and clinical laboratories.

5.2 TIME PERIOD OF DATA UNDER REVIEW

- Data will be reviewed from 02/01/2021 to 12/31/2026. Data will be collected prospectively as well as retrospectively using EHR records where available.
- Data will be reviewed from the start of data collected to the end of the study (up to 10 years from enrollment of the last study subject).
- All research data and related information will be retained in a secure access-controlled location for at least 2 years and up to 7 years (as required by certain sponsors) after completion of the study.

5.3 VARIABLES COLLECTED

- The following data points/variables will be collected: all variables captured by the medial chart review, questionnaires, CT/PET/MRI images and derived outcomes, accelerometry data, CGM, vital signs, anthropometrics, accelerometers, and biomarker assays.

5.4 SOURCE DOCUMENTS

- Study participant medical records, questionnaire, and outcomes data generated from the study will comprise the source documents.

5.5 DATA COLLECTION AND STORAGE

- **Secure storage:** Data will be collected via EHR or REDCap based questionnaires. All captured data will be housed in a HIPAA-compliant secure storage system, such as REDCap or Box, within the Cedars-Sinai network with access restricted to only approved members of the research team.
- **Limited Access:** Private identifiable information, will be accessible only to IRB approved study team members with current IRB training.
- **Unique ID Numbers**: Each patient will be assigned a unique ID number, as needed, for data merging.
- **Removal of Identifiers:** Direct identifiers (e.g., name or MRN) will be removed from any research records and destroyed as soon as scientifically possible and maintained only as long as necessary to abstract, analyze and verify data. Only de-identified coded data will be available for approved data analysts to perform statistical analyses.
- **Storage of Physical Records:** Any physical records for this study will be maintained at a secure location where access is limited to approved personnel. The records will not be removed from Cedars-Sinai premises.
- **Storage of Specimens**: Specimens will be maintained for this study at a secure location where access is limited to approved personnel.

5.6 CONFIDENTIALITY AND SECURITY OF DATA

To protect privacy, electronically stored data will be protected through stringent security measures and through the use of coded ID numbers and electronic security systems required by HIPAA. Paper documents will be scanned and saved on a secure network and also stored in locked cabinets in locked offices. Biological specimens will be stored and analyzed in locked areas with restricted access. Access to participants' data and biological specimens will be limited only to the study's investigators, clinical support staff for this study, the overseers of clinical facilities, and the study sponsor—all on a need-to-know basis.

6.0 DATA AND SAFETY MONITORING

6.1 DATA AND SAFETY MONITORING PLAN

The MPIs (Figueiredo, Peterson, and Salvy), study oncologists/surgeons, and the study dietitians will review the safety and progress of this study on an ongoing basis every 2-4 weeks throughout the duration of enrollment. The IRB will review this protocol on an annual basis for subject safety, and we will include results of the review in the annual progress reports submitted to NIH. The annual reports will include a list of adverse events and will address: (1) whether adverse event rates are consistent with pre-study assumptions; (2) reasons for dropouts from the study; (3) whether all participants met entry criteria; and (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study.

Each participant will be evaluated for adverse events using the PRO-CTCAE (self-report) and via extraction of adverse events from the medical record (clinical report). Any severe unanticipated adverse event will be immediately reported to the IRBs (within 48 hours of occurrence or recognition) and the NIH. All adverse events will be summarized annually and submitted to the IRBs and NIH. Any action resulting in a temporary or permanent suspension of this study (e.g., IRB actions) will be reported to the NIH. In the unlikely case of a pattern of unexpected adverse events, this change will be brought to the attention of the IRB for review, current and future participants will be notified of this change and stopping rules will be considered.

Quarterly safety reports will begin with a brief statement of the purpose of the study and a summary of the study design, including an organizational chart of all study personnel, as well as the projected timetable and targeted numbers for participant recruitment, intervention, and assessment. The study progress will be summarized, including enrollment, status, and retention of each cohort. In addition, a cumulative summary of the demographic breakdown of the sample will be summarized. Interim analyses will then be summarized. We will provide a detailed summary of any SAEs that have occurred since the previous Safety Report, including the participant name, nature of the event, date reported, action taken, resolution or ongoing complication(s) from the serious event, and whether the serious event was likely or unlikely related to participation in the study. There will also be a brief summary of SAEs that have taken place across the duration of the study. In addition, any major issues or problems encountered, and steps taken to correct or address them will be summarized. Finally, in the latter stages of the study when

it becomes relevant, the Safety Reports will also include a study summary, including a summary of the main findings, and procedures for preparing a report of study findings. Interim analyses of change in weight will be conducted, and the results summarized in the Safety Report.

The study's data safety and monitoring plan further includes the following components, overseen by the MPIs:

All Cedars-Sinai IRB policies and continuous reporting requirements will be followed in conducting the study. Any actions taken by the IRB as part of its continuing review will be immediately reported to NIH.

The MPIs will implement procedures to ensure that each participant provides informed consent and that all data remain confidential. In the case of a breach of confidentiality or other adverse event, the MPIs will report the event to the IRB and the appropriate NIH officials, and appropriate procedural changes will be implemented to prevent future breaches or adverse events.

6.2 DATA MONITORING AND QUALITY ASSURANCE

Adherence to the protocol, Good Clinical Practices (GCP), and institutional policy will be monitored by the contact PI during the course of the study through routine Disease Research Group (DRG) meetings (or equivalent). In addition, the SOCCI Cancer Clinical Trials Office (CCTO) Quality Management Core (QMC) will conduct focused internal monitoring visits and audits for data quality and protocol adherence. QMC reports will be forwarded to the SOCCI Data and Safety Monitoring Committee (DSMC). Refer to the DSMC Charter for more details. For any protocol, QMC has the authority to request more frequent reviews or focused safety monitoring if it is deemed appropriate for any reason.

6.3 SAFETY MONITORING

Oversight of the progress and safety of the study will be provided by the PI. The PI will maintain continuous safety monitoring for the duration of the study by reviewing subject/study data. Adverse events and unanticipated problems are not expected, but if they occur, they will be documented and reported according to CS-IRB policies and procedures. If the PI becomes aware of any new safety information that may place subjects at increased risk than what was previously known, the IRB will be promptly notified and if warranted, enrollment may be held until the PI determines whether a modification to the study is necessary and/or the informed consent documents are updated accordingly. It is the responsibility of the principal investigator to adhere to the Data Safety Monitoring Plan throughout the life of the study.

In addition, this protocol will utilize the SOCCI Data and Safety Monitoring Committee will provide another layer of data and safety oversight. DSMC membership and responsibilities are governed by the committee charter. The annual DSMC findings and

recommendations will be reported in writing to the Principal Investigator as a summary letter which will be forwarded by the Principal Investigator or designee to the CS-IRB. The DSMC may increase or decrease the frequency of study review, at their discretion. Refer to the DSMC Charter for details of the DSMC review.

6.4 MULTICENTER MONITORING PLAN

This trial will comply with the current requirements of the SOCCI Data and Safety Monitoring Committee. The SOCCI CCTO will be the Coordinating Center for this multicenter phase trial.

In accordance with the Data and Safety Monitoring Committee, investigators will conduct continuous review of data and patient safety. In addition, conference calls facilitated by the Study Lead at the Coordinating Center with investigators and staff at all participating sites will be scheduled at least monthly (and more often as needed) to discuss study progress. If there are no patients on treatment or in follow-up, email communication may be used in lieu of a teleconference, or in the circumstance where a scheduling conflict does not permit phone attendance. Meeting summaries will be included and document review of data and patient safety; meeting minutes will be submitted and reviewed by the DSMC.

All multicenter investigator-initiated trials conducted at the SOCCI are subject to data monitoring by the CCTO Quality Monitoring Committee (QMC). QMC has the responsibility for study monitoring for protocol compliance, data accuracy, performance of audits and monitoring of accrual (details found in the SOCCI Data Safety Monitoring Plan). All open trials are reviewed at a minimum once a year by the QMC (or more often depending on risk). This annual review includes the following: evaluation of the current accrual relative to the planned total accrual; examination of all reported violations; review of past monitoring visits and correspondence with the PI; review of previous correspondence between the PI and the QMC/DSMC. External sites will be notified of upcoming monitoring visits and will be expected to provide de-identified source documents for remote monitoring of patients, and/or access to the site EMR. Queries will be issued in the EDC and a detailed monitoring report will be provided to the participating site. The SOCCI CCTO will also forward any monitoring and/or auditing reports to the DSMC.

6.5 RECORD RETENTION

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, monitoring/auditing logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file in accordance with all applicable

federal guidelines and local guidelines.

Investigators will make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB, and Regulatory Agency (e.g., FDA) inspectors upon request.

Following closure of the study, each participating site will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

6.6 ADHERENCE TO PROTOCOL

The Investigator-sponsor will ensure that patient recruitment and enrollment, treatment, follow-up for toxicities and response, and documentation and reporting at SOCCI are all performed as specified in the protocol. At the UAB site, the Principal Investigator will assume the responsibilities for the day-to-day monitoring of the trial. Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, or a protocol exception request approved by the SOCCI Medical Director and IRB of record, the study shall be conducted exactly as described in the approved protocol.

6.7 EMERGENCY MODIFICATIONS

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, the IRB must be notified as soon as possible, but no more than 10 days from the investigator's awareness of the event.

6.8 PROTOCOL EXCEPTIONS AND ELIGIBILITY WAIVERS

A protocol exception is an anticipated or planned deviation from the IRB-approved research protocol, as described in the CSMC IRB Policy, Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement.. A protocol exception most often involves a single subject and is not a permanent revision to the research protocol. Protocol exceptions that extend beyond a single subject should result in a protocol amendment to avoid serial violations.

Planned exceptions to the protocol that are more than logistical in nature and/or impact an eligibility criterion, affect timing of study drug administration, or the investigator assesses the event may impact subject safety and/or study integrity, may not be implemented without prior IRB approval. The PI or her/his designee is responsible for submitting a protocol exception request and its supporting documents to the CSMC IRB if it meets the CS-IRB UPIRSO policy guidelines of a reportable exception/waiver. Study team should also refer to the IRB Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement guidelines to determine which deviations and

exception requests require IRB reporting. UAB will adhere to the policy of the IRB of record. Once IRB approved, the deviation or exception can be implemented.

Special considerations for Eligibility Waivers (EW)

In general, subjects who do not meet the eligibility requirements should not be enrolled. In the rare event that it is appropriate for subject inclusion, the rationale/justification and subject case history should be submitted to the IRB for approval. Such requests for minimal risk studies do not require prior review by the CCTO Medical Director.

6.9 OTHER PROTOCOL DEVIATIONS

Logistical deviations from the protocol (e.g., minor changes to the study schedule for an individual subject) do not require prior IRB approval unless the deviation has the potential to affect the subject's safety or study integrity. Such planned deviations that do meet this definition and do not affect the subject's safety or study integrity should be noted in the subject's research record or deviation log as described in the SOCCI CCTO's Standard Operating Procedure 12: Deviation and Noncompliance Reporting. For multi-site studies, follow local policy.

Unintentional deviations from the protocol that might affect subject safety or study integrity should be reported to the IRB within 10 days from when the investigator becomes aware that such a deviation has occurred, as outlined in the SOCCI CCTO's Standard Operating Procedure 12: Deviation and Noncompliance Reporting (or local policy, for multi-site studies). In this case, a Protocol Deviation report must be submitted in CS-IRB, per CSMC IRB policy, Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement. UAB will follow the policy of the IRB of record. All submissions should include a description of the plan to avoid similar deviations or exceptions in the future.

6.10 AMENDMENTS TO THE PROTOCOL

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation. Repeat exceptions or deviations to the protocol may suggest a protocol amendment is needed.

6.11 OBLIGATIONS OF INVESTIGATORS

The Principal Investigators are responsible for the conduct of the clinical trial at each site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigators are responsible for personally overseeing the treatment of all study patients. The Principal Investigators must assure that all study site

personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigators will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms and/or into a HIPAA-compliant study database. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

6.12 PUBLICATIONS

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

7.0 DATA MANAGEMENT & STATISTICS

7.1 BLINDING

All research staff and study investigators will be blinded, with the exception of S.J.S., the intervention counselors, and the study dietitian who will remain unblinded because of their required roles in delivering intervention counseling. Analyses of blood analytes will be performed by technicians who are blinded and not associated with the trial.

7.2 POWER CALCULATION

We powered the study using the two primary endpoints of the pCR rate and the average PRO-CTCAE score. Based on preliminary data, we estimated the pCR rate for the control arm to be 30%. For the average PRO-CTCAE score, we assumed asymptotic normality and calculated the minimum detectable difference/effect size (MDD/ES) at 80% power and using type 1 error rate of α=0.05 without correction for multiple endpoints. For a sample size of 135 completers per arm (n=270), the MDD in pCR is 17% (increase from 30% to 47%) using an exact binomial test and the MDES for the PRO-CTCAE score is 0.32 using a two-sided independent samples t-test with equal variance, which is a small-to-medium effect size. We expected to detect even smaller effect sizes when considering repeated measures of PRO-CTCAE. Assuming a 10% dropout rate, we will therefore enroll N=150 patients per arm in order to have N=135 completers.

We also performed a power calculation for one of the secondary outcomes: health-related quality of life (EORTC QLQ-C30). Assuming a within-group standard deviation of 23.9[2] and a sample size of 135 participants per arm, we calculated MDDs of 10.3, 9.0, 7.3, and 5.2 for ICCs of 0.2, 0.4, 0.6, and 0.8, respectively, using a two-sided independent samples t-test with equal variance at a power of 80% and a type 1 error rate of α=0.05.

7.3 STATISTICAL ANALYSES

All analyses will be performed blinded using two-sided tests and α=0.05 in the software program *R*. The primary analyses of clinical outcomes will be intention-to-treat. We will also perform a secondary per-protocol analysis using marginal structural models with inverse-probability-of-treatment weighted (IPTW) estimators to describe treatment effect as a function of levels of adherence.

Descriptive statistics will be presented for both quantitative and qualitative variables. Contingency tables for treatment and toxicity data aggregated by grade, system, or term will be summarized with correspondence analysis.

In the primary analysis, we will test differences in pCR using a Fisher's Exact test. We will calculate the PRO-CTCAE average over items at specific time points as the response variable of a multivariable linear mixed model using baseline average PRO-CTCAE, group, time, and interaction between group and time as covariates. Furthermore, we will consider include additional potentially relevant covariates, such as sex, age, race, stage, surgical status, and treatment modality. Random effects will describe the correlation within repeated measures and sites. We will also test the interaction of group with sex, age, surgical status, and treatment modality. In the presence of interaction effects, we will perform subgroup analyses with Holm correction for multiple groups.

As a secondary analysis of toxicity, we will calculate the Toxicity Index (TI) using CTCAE data, using on methods proposed in Rogatko et al.[3]. Following Gresham et al.[4], we will fit a multivariable probabilistic index model, which is a generalization of the Mann-Whitney test, where the toxicity index is the response variable and we will consider adjusting by sex, age, race, stage, surgical status, and/or treatment modality. Furthermore, we will calculate the toxicity index for subcategories of treatment-emergent adverse events (e.g., gastrointestinal).

For other outcomes, Multivariable Generalized Additive Models for Location, Scale and Shape (GAMLSS) will be fitted. In particular, GAMLSS will be fitted to total quality of life scores and subscores as response variables and group, time, and interaction between groups and TRE will be covariates. We will also adjust for any relevant and impactful covariates, such as sex, age, race, stage, surgical status, and treatment modality as fixed effects. Random effects will be added to consider the correlation from repeated measures and different sites. Adequate probability distribution for the response variable will be defined based on diagnostic plots and the AIC. These methods will also be applied to analysis of IGF-1 and the ratios of IGF-1 to its two binding proteins as the response variables. Furthermore, the molecular outcomes (γ-H2AX, Ki67, caspase-3, LC3-I/II, and total antioxidant capacity) will be analyzed with adjustment for multiple endpoints using the Hochberg correction, assuming the markers are positively correlated.

To test the hypothesis that IGF-1 mediates changes in molecular endpoints, mediation analysis will be performed based on linear regression models with normal errors: (1) the outcome model will be defined with the change in blood analytes as the response variable and group and the change in IGF-1 as covariates; and (2) the mediator model will be defined with the change in IGF-1 as the response variable and the group as a covariate. Average mediation and direct effects will be calculated with the control arm as the reference, following methods in Imai et al.[5], assuming no interaction between group and the mediator and assuming sequential ignorability. Baseline covariates (e.g., sex, age, race, stage, surgical status, and treatment modality) will be considered in the

model to strengthen the validity of sequential ignorability, and sensitivity analyses will be performed for both assumptions.

We will also adopt the same modelling strategy based on GAMLSS for mood (e.g., NIH PROMIS t-scores), psychosocial functioning, sleep (accelerometry and PSQI), daily activity counts and intensity (accelerometry), and dietary intake (calorie intake, macronutrient composition, Healthy Eating Index, added sugar, fruits and vegetables, solid fats, alcoholic beverages, sodium, and fat). To test how mood, psychosocial functioning, sleep, activity, and dietary intake moderate the relationship between the intervention arms and clinical outcomes, we will add interaction terms to the model, as described above. If the interaction effects are statistically significant, then we will interpret the data using a graphical approach. To draw the graphs, we will use the "pick-a-point' approach[6]. This approach involves selecting representative high and low values (mean ± 1 SD) of the moderator variable and then estimating the effect of the focal predictor at those values.

Finally, patterns of missing data will be analyzed, and missing values for covariates will by imputed using multivariate imputation by chained equations under the assumption of missing data at random (MAR). The plausibility of imputed values will be checked by corresponding diagnostics. The outlined statistical analysis will be performed for each imputed dataset and results will be pooled according to Rubin's Rule. In addition, we expect that patients who decrease well-being might dropout over time. Therefore, a sensitivity analysis will be performed to evaluate the robustness of the MAR assumption and departures towards Missing Not at Random (MNAR) assumption considering scenarios to assess the robustness of the results.

8.0 STUDY MANAGEMENT

8.1 CONFLICT OF INTEREST

Any reportable conflict of interest will be disclosed to the local IRB and will be outlined in the Informed Consent Form.

8.2 INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL AND CONSENT

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. A reliance agreement will be utilized to permit Cedars-Sinai to be the IRB of record (reviewing IRB) and the University of Alabama at Birmingham will be the relying institution. In accordance with the reliance agreement, all pertinent study documents (i.e., protocol, ICF) will be reviewed and approved by the Cedars-Sinai IRB prior to study initiation. The investigators will comply with the applicable regulatory requirement(s) and adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

8.3 REGISTRATION PROCEDURES

Eligibility Verification

Prior to registration, all subjects must undergo an eligibility verification by the study-specific research staff. Minimal risk studies are exempt from SOCCI Quality Management Core (QMC) central eligibility checklist review and eligibility verification.

QMC central eligibility checklist review and eligibility verification for all subjects enrolled is performed only if requested by the PI at any time during the life of the study.

Registration
After eligibility is verified, each site will assign the subject a study number and site staff will then register the patient in OnCore® and/or REDCap

All subjects that sign informed consent will be assigned a subject number sequentially by their date of consent. Those subjects who are consented to participate in the clinical trial but do not meet one or more criteria required for participation during the screening phase will be listed as screen failures on the master list of consented subjects. Eligible subjects, as determined by screening procedures and verified by a treating investigator, will be registered on study at Cedars Sinai Medical Center by the Study Coordinator.

Issues that would cause treatment delays after registration will be discussed with the Principal Investigator (PI). If a patient does not receive protocol therapy following registration, the patient's registration on the study will be canceled.

Assignment of Subject ID: The study teams will track all subjects who sign consent using OnCore and/or REDCap. Subjects found to be ineligible will be recorded as screen failures. Subjects found to be eligible will be registered using a lead-in number of 01, followed by a three-digit numeric ID that follows the standard SOCCI format (001, 002, etc.). Subjects found to be eligible at the University of Alabama at Birmingham (UAB) site will be registered using lead-in number of 02, followed by a three-digit numeric ID that follows the standard SOCCI format (001, 002, etc.). At UAB, only limited patient information will be entered into OnCore (i.e. updating status to enrolled).

Subject ID's will follow the format below:

Cedars-Sinai Medical Center

Screening 11, 12, 13, 14, Enrolling CSMC-001, CSMC-002

The University of Alabama at Birmingham

Screening 610-1, 610-2, 610-3 Enrolling UAB-001, UAB-002

Registration is completed as follows:

Assignment of a patient study number

Assignment to the patient a dose/treatment arm as determined through communication with Biostatistics and the principal investigator, if applicable

Enter the patient in OnCore

8.5 DATA MANAGEMENT AND QUALITY CONTROL AND REPORTING

REDCap is the Cedars-Sinai Cancer institutional choice for the electronic data capture of case report forms for SOCCI Investigator Initiated Trials. REDCap, a HIPAA-compliant database, will be used for electronic case report forms in accordance with institutional requirements, as appropriate for the project. The Study Staff will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

9.0 REFERENCES

1. Marinac CR, Nelson SH, Breen CI, et al. Prolonged Nightly Fasting and Breast Cancer Prognosis. JAMA Oncol 2016;2:1049-55.
2. Han CJ, Gigic B, Schneider M, et al. Risk factors for cancer-related distress in colorectal cancer survivors: one year post surgery. J Cancer Surviv 2020.
3. Rogatko A, Babb JS, Wang H, et al. Patient characteristics compete with dose as predictors of acute treatment toxicity in early phase clinical trials. Clin Cancer Res 2004;10:4645-51.
4. Gresham G, Diniz MA, Razaee ZS, et al. Evaluating Treatment Tolerability in Cancer Clinical Trials using the Toxicity Index. J Natl Cancer Inst 2020.
5. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. Psychological methods 2010;15:309.
6. Rogosa D. Comparing nonparallel regression lines. Psychological Bulletin 1980;88:307-321.
7. Hays RD, Gresham G, Ganz PA, Tighiouart M. Comparison of Simple-Summated Scoring and Toxicity Index Scoring of Symptom Bother in the NSABP B-30 Clinical Trial. Applied Research in Quality of Life. 2022 Sep 9:1-1