Time-restricted eating in cancer survivorship: A single-arm feasibility pilot study

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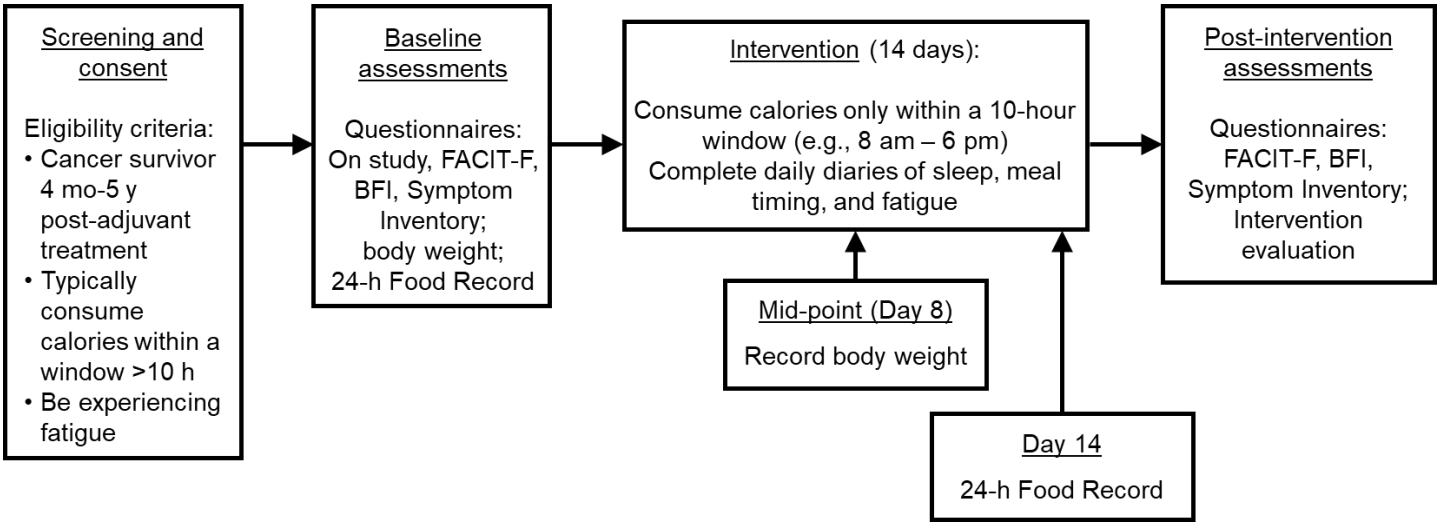
Figure 1. Study Schema



1. Purpose of the study

In this study, the feasibility of delivering a time-restricted eating (TRE) intervention among fatigued cancer survivors will be assessed. The participants will be asked to eat *ad libitum* only within a self-selected 10-h window each day for 14 days, and exploratory measures of fatigue, well-being, and other symptoms will be collected at baseline and post-intervention. These feasibility data will be used as preliminary data for a grant proposal addressing one of NCI's Provocative Questions: "How does intermittent fasting affect cancer incidence, treatment response, or outcome?"[1]

The feasibility of conducting a 10-h TRE intervention among cancer survivors will be evaluated using the following specific aims:

Primary Aim: to assess the adherence of the participants to the 10-h TRE intervention. This will be determined by the percent of days that each participant adheres to the 10-h TRE dietary pattern over the course of the 14-day intervention.

Secondary Aim 1: to assess the retention of participants during the 10-h TRE intervention. This will be determined by the percent of consented participants who provide baseline and post-intervention assessments.

Secondary Aim 2: to assess the safety of the TRE intervention. We will closely monitor instances of adverse events as described by the Common Terminology Criteria for Adverse Events (CTCAE), version 5,[2] with a special focus on body weight.

Secondary Aim 3: to describe the feasibility of recruiting cancer survivors to a 10-h TRE intervention. The number consented over the number approached will be calculated, and the population (i.e., those approached) will be characterized based on eligibility and willingness to participate.

2. Background and rationale

Cancer-related fatigue affects at least 30-90% of patients undergoing chemotherapy, depending on the type of cancer and treatment as well as the diagnosis method.[3,4] It is not relieved by sleep or rest, and its severity can greatly hinder the ability to perform activities of daily living and decrease quality of life. The mechanisms behind the etiology and pathophysiology of cancer-related fatigue seem to be related in part to inflammation, hypothalamic–pituitary–adrenal (HPA) activation dysfunction, metabolic and/or endocrine dysregulation, or other mechanisms, but are largely not understood, thereby thwarting the development of effective preventative strategies and treatments.[5]

Circadian rhythms are biological diurnal cycles that work in synchrony to regulate hormone secretion, the sleep/wake cycle, core body temperature, and other processes. Circadian rhythm and human health have a bidirectional relationship, and circadian disruption is associated with a broad range of pathologies including, purportedly, cancer-related fatigue.[6-8] Circadian regulation occurs via genetic and physiological processes, and is important to maintain homeostasis of the endocrine system, autonomic nervous system, and nutrient metabolism.[9,10] The importance of maintaining circadian rhythm is clear when traveling across time zones, and "jet lag" is a common experience of fatigue when the circadian clock is disrupted.[10] Our group (Division of Cancer Control) has demonstrated that chemotherapy disrupts circadian rhythm, and that changes in circadian rhythm are associated with fatigue.[8] Further, research from our group has shown that yoga can help regulate biobehavioral oscillations of circadian rhythm and, consequentially, improve sleep and reduce fatigue.[11]

Regulation of circadian rhythm relies heavily on regular sleep habits, and interventions to regulate circadian clock currently include light therapy, exercise, melatonin supplementation, and more recently,

nutrient timing.[10] Indeed, there are consistent animal and human data demonstrating that aberrant feeding/eating patterns dysregulate objective circadian clock measures (i.e., expression of genes that show strong diurnal oscillations).[12] In an observational study among 156 healthy American adults in California, Gill and Panda[13] showed **that approximately 50% of people eat within a window greater than 14.75 hours per day**; only 10% eat within a window 12 hours or less.[9] It is unknown but likely that eating patterns are similar among American cancer survivors. A consistent, shorter window of eating, for example 10 hours or shorter, may aid in the regulation of the circadian clock and improve metabolic homeostasis with broad health outcomes.[9,14,15] Restricting eating to certain time window is called "time-restricted eating" (TRE).

TRE as a therapeutic approach has garnered a large appreciation in the literature and in the public in the last decade for its ability to mediate the circadian clock and prevent and treat various pathologies.[14,15] TRE involves restricting the consumption of calories to a short window (4-12 hours) during normal waking hours, for example 8am-6pm; water is never restricted. Human (time-restricted eating) and rodent (time-restricted feeding) studies have shown that TRE helps to maintain metabolic homeostasis and, as a result, prevents excess body weight, improves sleep, and attenuates age- and diet-induced heart disease (review[15]). One study clearly demonstrated the effects of nutrient timing on metabolic regulation: time-restricted feeding vs. time-unrestricted feeding of mice led to weight loss despite equal energy intake.[16] In humans, Gabel et al. performed an 8-h TRE study among obese adults for 12 weeks (n=23).[17] Despite the diet being *ad libitum*, caloric intake decreased 341±53 kcal/day. Body weight decreased 2.6±0.5%, and systolic blood pressure decreased 7±2 mmHg. However, there were no significant changes in body composition, circulated lipids, fasting blood glucose, or fasting insulin. Also, Wilkinson et al. performed a 10-h time restricted eating study among patients with metabolic syndrome for 12 weeks (n=19).[9] They observed improvements in sleep efficiency and quality, a safe rate of decrease in body weight and body fat percentage, a reduction in total and low density lipoprotein (LDL) cholesterol, and reductions in systolic and diastolic blood pressure.[9] While these studies were implemented for 12 weeks, benefits have been seen in glucose and lipid metabolism and circadian clock gene expression in as short as 4 days.[18]

To date, TRE has only been studied in healthy participants or those who are overweight, obese, or with metabolic syndrome (Wilkinson et al.[9] and references within). These studies have collectively shown that a 10-h TRE window is feasible, safe, and effective at improving metabolic markers among their respective populations. Thus, the next logical step is to prudently begin to apply a dietary pattern intervention to cancer survivors with the ultimate goal of evaluating its effectiveness to treat cancer-related fatigue. Thus, herein, a single-arm pilot TRE study will be conducted among cancer survivors to assess the feasibility of recruiting participants to a TRE intervention and adherence of survivors to a 10-h TRE window for 2 weeks. These data will serve as preliminary data for an R21 grant application in response to a Provocative Question posed by the NCI: "PQ2: How does intermittent fasting affect cancer incidence, treatment response, or outcome?"[1] If this single-arm pilot study is successful, the grant application will propose a randomized controlled trial evaluating the preliminary efficacy of TRE vs. longer eating windows to alleviate cancer-related fatigue among cancer survivors.

3. Administrative organization

We will be recruiting subjects from the Wilmot Cancer Institute. Participants will be approached in the oncology clinics where cancer survivors have routine follow-up appointments. Alternatively, patients referred to the study team by the treating provider may be called, emailed, or sent a letter giving them basic information about the study. These clinics include Wilmot Cancer Institute, Pluta Cancer Center, or another Wilmot satellite location. Private areas in any of these locations may be used to consent the participant and

do study assessments. Participants will also be asked to complete some of the assessments at home. As an alternative to clinic visits, this entire study can be completed remotely.

4. Study design

4.1 Brief description and specific aims

This will be a single-arm feasibility pilot study among 40 cancer survivors with moderate to severe baseline fatigue. All participants in this study will be asked to follow a TRE meal pattern for 14 consecutive days. Participants will be encouraged to consume food and beverages only within a 10-h time window for the 14-day intervention, with the exception of water, which will be encouraged at any time. Participants will be allowed to take any of their normal medications at the prescribed times. Participants will be asked to complete a daily diary (every day for 14 days, approximately 1 min each day), as described in §4.4. At baseline, mid-point, and post-intervention, participants will be asked to record their body weight with a scale that the study team will provide. Also at baseline and post-intervention, participants will complete questionnaires related to their fatigue, quality of life, symptoms, and a 24-h food recall (approximately 10 min). Post-intervention, we will conduct an exit interview with each participant about their experience with the intervention (10-30 min).

Primary Aim: to assess the adherence of the participants to the 10-h TRE intervention. This will be determined by the percent of days that each participant adheres to the 10-h TRE dietary pattern over the course of the 14-day intervention.

Secondary Aim 1: to assess the retention of participants during the 10-h TRE intervention. This will be determined by the percent of consented participants who provide baseline and post-intervention assessments.

Secondary Aim 2: to assess the safety of the TRE intervention. We will closely monitor instances of adverse events as described by the Common Terminology Criteria for Adverse Events (CTCAE), version 5,[2] with a special focus on body weight.

Secondary Aim 3: to describe the feasibility of recruiting cancer survivors to a 10-h TRE intervention. The number consented over the number approached will be calculated, and the population (i.e., those approached) will be characterized based on eligibility and willingness to participate.

4.2 Participant population

In total, 40 cancer survivors will be recruited. Participants will be recruited from Wilmot Cancer Institute including satellite clinics (e.g., Pluta Cancer Center) and will have medical clearance from their provider. From previous local studies completed by the Division of Cancer Control, a 20% rate of attrition is expected, resulting in approximately 32 participants with evaluable data.

No special classes of participants such as fetuses, neonates, children, pregnant women, prisoners, institutionalized individuals, or decisionally impaired adults will be recruited.

Total planned enrollment: 40 participants

Targeted/planned enrollment by ethnic and racial categories:

Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	2	1	3
Not Hispanic or Latino	25	12	37
Ethnic Category: Total of All Participants	27	13	40
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	4
White	24	10	34
Racial Categories: Total of All Participants	27	13	40

Males and females will be recruited to this study. However, there is an expectation to recruit more females than males because Pluta Cancer Center will be a major recruitment site and Pluta houses the Comprehensive Breast Care program. Based on the participant characteristics of recently completed local studies by our Division, it is anticipated that the potential sample pool for the current study will be mostly white/non-Hispanic individuals, though participants of other racial and ethnic groups will be encouraged to participate. The average age for studies conducted by our Division tends to be approximately 55-65 years, and it is expected to be similar for this study, too. Children, individuals under the age of 18, as defined by the NIH Grants Policy Statement, will not be included because their meal timing is often determined by their parents/guardians/caregivers.

4.3 Study interventions

This will be a single-arm, feasibility pilot study that recruits 40 cancer survivors. After screening and consent, participants will complete an on-study form and baseline questionnaires: the Functional Assessment of Chronic Illness Therapy (FACIT-F), Brief Fatigue Inventory (BFI), the 27-item modified MD Anderson Symptom Inventory, and a 24-h Estimated Food Record. These questionnaires can be completed either online via REDCap or on paper (participant's choice) and take less than 10 min total to complete. Participants will be provided with a small bathroom scale, with which they will be asked to report their weight at baseline (Day 1), mid-point (Day 8), and post-intervention (Day 15). We prefer that body weight is measured at home, in the morning, before food or drink is ingested, without clothing. Before the intervention period, all participants will be instructed as to how to follow a TRE diet pattern. The TRE window will be 10 hours long and will be selected by the participant based on their normal meal patterns and preferences. For example, the window could be 7am-5pm, 8:30am-6:30pm, or 12:00pm-10:00pm. However, the window should not change during the intervention period. Every day for 14 days, participants will be asked to consume food and beverages only within the 10-h window; water will be allowable any time. Because of the potential of caffeine and artificial sweeteners to affect circadian rhythm,[19,20] coffee, tea, chewing gum, and diet beverages will be discouraged during the fasting window. Also for these 14 days, participants will complete a daily diary at the end of the day noting the time they wake up, the time

of their first calorie, the time of their last calorie, the time they go to bed, and their average fatigue level for the day.

There will be an emphasis on honesty over adherence, and participants' experiences will be used to improve the intervention in a larger, future study. Post-intervention, the participants will be asked to complete the same questionnaires as baseline (i.e., FACIT-F, BFI, Symptom Inventory, 24-h Estimated Food Record), and body weight will be measured. An exit interview will be conducted to assess what the participants did and did not like about the intervention; if they think it improved their symptoms, sleep quality, or quality of life; what tips they have for future participants; if they would recommend the eating pattern to friends; or any other constructive comments. This interview will last 10-30 min, and it will be audio-recorded with explicit permission.

Participants will have the option of completing all the questionnaires and daily diaries electronically or on paper. Similarly, exit interviews can be completed on-site or via phone according to patient preference. Participants will be compensated for their time $10 for baseline assessments, $10 to complete daily diaries, and $10 for post-intervention assessments for a total of $30 maximum.

All questionnaires will be scored and entered into a secure database by the study team. Adherence will be the primary end-point; it is expected that participants will be able to eat within the 10-h window at least 5-6 out of 7 days per week,[17,21] or 11/14 days (78.6% adherence). In regard to retention, we expect that at least 32/40 (80%) of participants who complete baseline assessments will complete post-intervention assessments. Changes in quality of life and fatigue will be assessed over time as exploratory measures.

4.4 Study outcomes/endpoints

The primary aim of this study is adherence, as assessed using daily diaries. How many days the participants were able to restrict their eating to the 10-h window will serve as the primary endpoint. The daily diary will include the time of the first calorie consumed and the time of the last calorie consumed every day for the 14-day intervention. Success will be defined by the participants reaching the fasting target at least 11 of the 14 days on average. This goal is reasonable based on a study by Kesztyüs et al.,[21] whose participants adhered to this dietary pattern 85.5 ± 15.2% of days over a three-month intervention, and a study by Gabel et al.,[17] whose participants adhered 5.6 ± 0.3 days/week (80%) for 12 weeks on average.

A secondary aim is retention; it is expected that at least 80% (32 out of 40) of those who provide baseline data also provide post-intervention data.

Another secondary aim will be safety. We hypothesize that body weight will be maintained within 5% of baseline throughout the intervention and that there will be no adverse events that are Grade 2 or worse that are attributable to the intervention.[2] To ensure safety in regard to weight loss, body weight will be measured three times: baseline (Day 1), mid-point (Day 8), and post-intervention (Day 15). Body weight will be measured by the participant by a scale that is provided, and then reported on the daily diary (e.g., BalanceFrom Digital Body Weight Bathroom Scale). To ensure consistent and reliable measures, participants will be asked to weigh themselves in the morning, before eating or drinking, with minimal clothing. The scale should be placed on a hard, level surface (e.g., tile, wood) that is the same for each measurement, if possible, because there can be slight variations in measurements if the scale is placed on a rug vs. a hardwood floor, for example. Participants will have the option of keeping the scale at the end of the study.

To ensure safety in regard to adverse events, we will closely monitor all adverse events as described by the CTCAE, version 5.[2] Adverse events that will be of particular interest due to potential causality include weight loss or weight gain (see §9.1.1), dizziness, and exacerbation of fatigue.

Also, to ensure safety in regard to caloric intake, participants will complete a 24-h Food Record before the intervention (their normal diet and dietary pattern). This will be done prospectively on any day before they begin the TRE intervention. The 24-h Food Record entails noting the identity of the food, the quantity, and the time it was ingested. They will also complete a prospective 24-h Food Record, including times, on Day 14, the last day of the intervention. The Food Record will be analyzed for total calories, macronutrients, micronutrients, and bioactive compounds using Nutrition Data System for Research (NDSR; Regents of the University of Minnesota, Minneapolis, MN) or a similar program.

An exploratory aim of this study is cancer-related fatigue, as assessed using the FACIT-F, BFI, and Symptom Inventory. Patients will complete these instruments at baseline and post-intervention.

1. Functional Assessment of Chronic Illness-Fatigue (FACIT-F) questionnaire: The FACIT-F is a 40-item, validated, commonly used measure of fatigue that is comprised of five subscales: physical well-being, social well-being, emotional well-being, functional well-being, and fatigue.[22] It captures symptoms in these categories over the last 7 days.
2. Brief Fatigue Inventory (BFI): The BFI is a 10-item fatigue questionnaire that is also validated and commonly used.[23] It captures fatigue *now* and the usual and worst in the last 24 h. It also includes 6 single-item questions regarding how fatigue has interfered with general activity, mood, work, etc.
3. Symptom Inventory (SI): The symptom inventory (modified from the MD Anderson Symptom Inventory[24]) includes 19 items that are common in the cancer experience (e.g., pain, distress, lack of appetite, numbness and tingling, fatigue), as well as 8 items related to how much these symptoms interfere with activities of daily living and quality of life. As many symptoms often correlate with each other including fatigue (i.e., symptom clustering[25]), it is important to capture the change in many symptoms from baseline to post-intervention. Exploratory analyses will probe whether adherence to the diet or high consumption of any dietary component correlates with the change in any of these symptoms over the two-week intervention.

There are a total of six questionnaires and survey assessments that will be completed. The on-study form will be completed at baseline only; the daily diary will be completed during the intervention; the others will be completed at baseline and post-intervention:

- On study (demographics and clinical characteristics; baseline only)
- FACIT-F (Fatigue and quality of life)
- BFI (fatigue)
- Symptom inventory
- 24-h Food Record
- Daily diary

The 3-4 questionnaires that will be completed at baseline and post-intervention should take approximately 10 min in total to complete. The daily diary will take less than 1 min to complete each day. The 24-h Food Record will require noting the time, identity, and quantity of food eaten throughout one day.

4.5 Timeline

Upon opening of the study, we expect that approximately 4-8 participants will be recruited per month for approximately 8 months. Data will be entered as they come in, and data analysis will take place soon thereafter. These data will be used to inform a follow-on randomized clinical trial for which a grant

will be submitted in the Summer 2020.[1] It is also anticipated that one manuscript will also emerge from this study, which will be submitted for publication within one year of the study closing.

4.6 Design considerations

Why a 10-hr TRE pattern? Intermittent fasting has gained a lot of interest in the last decade due to its strong pre-clinical data supporting its ability to regulate circadian rhythm, improve homeostatic metabolism, and alleviate age-related morbidities.[14] The investigators and the NCI believe that it will be a promising lifestyle intervention to alleviate symptoms of cancer and side effects of treatment.[1] Intermittent fasting protocols include more extreme patterns (e.g., alternate day fasting,[26] as well as TRE with shorter time windows, such as 4-h[27]). However, most human studies thus far have been performed among healthy participants, and especially participants who are overweight. It is hypothesized that 10 hours is the longest window that can be implemented that will be safe, effective, and not too uncomfortable for the participants. With a 10-h window, none of the three traditional meals (e.g., breakfast, lunch, dinner) have to be "skipped," though meals might need to be shifted. The primary goal is for the diet pattern in this line of research is to regulate circadian rhythm, not induce caloric restriction.

Why in survivorship vs. during adjuvant treatment? Participants will be recruited 4 months–5 years after chemotherapy, surgery, and/or radiation for curative intent. Thus, their immediate, acute side effects of treatment will have subsided though persistent side effects will still be present. It is thought that survivors will have enough physical and mental resources to adhere to a change in diet pattern, while patients actively undergoing treatment will have a much harder time.

Why a 14-day duration? Studies that have implemented TRE interventions have used a wide range of intervention lengths, from 4 days[18] to 12 weeks.[17] The 4-day intervention had a positive effect on 24-hour circulating glucose concentrations, lipid metabolism, and circadian rhythm clock gene expression.[18] Other nutrition interventions, such as a Mediterranean Diet, have shown measurable effects on vigor (similar to fatigue) in 10 days.[28] The main outcome herein is feasibility to recruit and retain participants, and it is thought that 14 days is an appropriate amount of time to know if someone will be willing to adhere to a short-term lifestyle change. Two weeks includes two full weeks including weekends, and is thus better than 10 days so that the presence (or absence) of weekend social activities during the intervention is not a biasing factor.

Should we directly monitor glycemia? It is possible that this intervention could lead to hypoglycemia among individuals who are at risk due to the presence of type 1 diabetes mellitus and, especially, use of insulin therapy.[29] However, specific research addressing this question has shown that various regimens of TRE and intermittent fasting *do no*t lead to hypoglycemic events in the vast majority of individuals studied, including those with type 2 diabetes.[30,31] In fact, TRE shows glycemic benefits for individuals with prediabetes[32] as well as overweight individuals.[18] Specifically, Singh et al. recruited 32 patients with a high risk of cardiovascular disease (nine with type 2 diabetes); participants consumed the vast majority of their calories in the evening (a calorie restrictive protocol that is more extreme that the one proposed herein) including no breakfast and there were no hypoglycemic episodes.[30] In addition, Arnason et al. encouraged 10 patients with type 2 diabetes who were taking metformin consume all their food within a 4-6 hour eating window (shorter than the proposed 10-hour window); they observed zero instances of hypoglycemia and concluded that the regimen was safe for this population.[31] Thus, we are excluding individuals on insulin therapy, and we will require approval from each potential participant's oncologist. In the sign-off form, we will emphasize that he or she should reach out to the primary care provider to ensure that the patient is not in this "high risk" group.

5. Inclusion and exclusion criteria

Participants will be selected to represent a broad range of patients with varying demographics, incoming metabolic functioning, and clinical cancer characteristics. This study will not be powered for any subgroup analyses.

Inclusion criteria (Participants must…):

1. Have completed adjuvant chemotherapy, surgery, and/or radiation for cancer at least 4 months and not more than 5 years prior to enrolling,
2. Have a baseline level of fatigue, as determined by reporting a score of 3 or higher for the question, "In the last week, how bad was your worst fatigue on a scale from 0-10?"
3. Be able to speak English,
4. Be at least 18 years old,
5. Be willing and able to adhere to study procedures, and
6. Be able to provide informed consent.

Exclusion criteria (Participants must not…):

1. Already eat all their food within a window that is 10 h or shorter most (6/7) days of the week,
2. Be underweight, as defined as a body mass index $\leq$20.0 kg/m^2,
3. Not have surgery planned in the next month,
4. Not have any contraindications to the proposed nutrition intervention as identified by their medical provider, their designee, or the study team (e.g., type 1 diabetes, risk for hypoglycemia, medication requirements, pregnancy, breastfeeding,[33] recent history of an eating disorder),
5. Not be taking insulin, or
6. Be on enteral or parenteral nutrition.

Cancer survivors may be taking hormone therapy, immune targeted therapy (e.g., Herceptin), or another type of therapy to prevent recurrence.

6. Recruitment methods

6.1 Identification and recruitment

Dr. Kleckner or a member of the study team will recruit participants using the Cancer Control group's established procedures. Before recruitment approval will be obtained by the James P. Wilmot Cancer Institute Clinical Trials Peer Review and Monitoring Committee (PRMC) as well as the University of Rochester Medical Center (URMC) Research Subject Review Board (RSRB). Potential participants will be identified using three methods: (1) screening medical records, (2) direct referral from providers (e.g., nurses and physicians), and (3) flyers.

6.1.1 Identification and recruitment via medical records

Potentially eligible participants receiving care at the URMC will be identified in a HIPAA-compliant manner by study personnel via review of scheduled outpatient appointments. The study team will then review any potential candidates. Medical records typically show time since completion of adjuvant

therapy (e.g., surgery, chemotherapy). If an individual appears to be eligible, the study team will contact the treating provider (or a designee) to notify them of a potential candidate and obtain approval to speak with the patient. The provider (or a designee) will approach the potential participant at a regularly scheduled oncology appointment. This initial contact will assess whether the participant has any interest in participating in a clinical trial to investigate the feasibility to implement a TRE dietary intervention. If the person is interested, the provider will refer the individual to the study team. The study team will then meet with the candidate in a private room to discuss the study activities in detail and review eligibility (either that day or at a later date). If the person is eligible, study personnel will explain the details of the study. Study personnel can obtain informed consent right then or at a later date from those who agree to participate. After consent is provided, the participant will be provided with study materials.

6.1.2 Identification and recruitment via direct referral from physicians, physician assistants, and nurses

The study team is working with several oncologists (including, but not limited to the medical monitor Dr. Dunne) and his medical team (e.g., nurses, physician assistants) to identify potential patients at the University of Rochester who are likely eligible for our study. If the patient is eligible based on information in the medical records and from the physician and medical team, the provider will be asked to refer the person to the study team (or obtain the physician's permission to contact the person) to discuss this study.

6.1.3 Flyers

A flyer advertising our study will be placed in locations designated for such use. Cancer survivors can contact a member of the study team directly for more information. Their medical provider will be contacted to ensure that the intervention is appropriate for the potential participant before consenting them.

6.2 Screening

For convenience to the potential participant, the person's clinic appointment might be combined with their screening and consent, or participants can undergo the screening and consent process remotely via eConsent. To protect the privacy of potential participants, face-to-face recruitment discussions will be conducted in a private location.

Dr. Kleckner or a member of the study team will meet the potential participant in person or talk to them over the phone to explain the project and invite them to participate. It is expected that some patients will decline to participate, and some will not be eligible;[13] approaching the same individual twice will be avoided by keeping a screening log containing the following information:

- Screening ID (1, 2, 3,…)
- Name
- Date of contact
- Medical record number
- Where/how we talked to the potential participant (e.g., clinic location, phone)
- Whether the patient was eligible or not
- If ineligible, the reason they are ineligible
- Whether the patient ultimately consented or declined
- If declined consent, the reason for declining consent

- If consented, the participant ID in the study (e.g., 101, 102, 103, …)

Patients will need medical clearance from their provider to participate in the study.

7. Consent process

7.1 Written consent

For participants who are interested in participating, a member of the study team will meet with the potential participant in a private room. She or he will go through the consent form with the patient face-to-face to ensure comprehension. They will then be given the option to sign the consent form. Dr. Kleckner (study chair) will be available to answer any questions the potential participant may have about any aspect of the study prior to consenting and throughout the entire study period. The participants will also have access to the dietitians at the Integrative Oncology and Wellness Center at Pluta Cancer Center (e.g., Sue Czap, RD) if they have other diet-related questions. Potential participants will be allowed to take the consent form home to think about and discuss with family or friends; each potential participant will have sufficient time to consider participation. To minimize coercion, the study team will emphasize that participation is completely voluntary and their cancer care will not be affected by their participation in the study.

7.2 eConsent

In lieu of the paper-based consent document, consent may occur remotely using the RSRB-approved eConsent document provided via REDCap. The study staff will screen for potential participants using the above screening procedures and initiate initial contact via the following methods: 1) the treating oncologist or a member of the medical team (e.g., nurse practitioner) will introduce the study to the participant via a clinic appointment (in person or telehealth) and inquire if it would be okay for our study team to contact them, 2) with approval of the treating oncologist or a designee, a recruitment letter will be mailed to the potential participant briefly describing the study and asking them to contact us if they would like more information, and 3) with approval of the treating oncologist or a designee, a message will be sent to the potential participant via eRecord (myChart) briefly describing the study and asking them to contact us if they would like more information. If a potential participant is interested, the study team will talk to the person on the phone and obtain verbal permission from the patient to send a copy of the eConsent via email or text message stating, “Because URMC can’t control the security of email or text messages once we send them, we need your permission to text or email you. Do you want to receive a copy of the consent document and a link to the eConsent via text or email?” Verbal permission from the patient will be documented. We will email or text the eConsent in the form of a pdf document and set up a phone call or Zoom meeting (participant’s choice) to formally go over the consent document. In a separate email or text, we will provide a link to the eConsent document as well as instructions on how to access the eConsent—we will use verification with a passcode based on known information (e.g., the patient’s home zip code). No personal health information will be sent via any emails/texts. The eConsent documents may be viewed on computers, electronic tablets, or smartphones. The pdf copy of the eConsent and the REDCap eConsent will have identical information; it will be optional for the person to review the consent before the study team discusses it with them. After a member of the study team reviews the consent document with the participant over the phone or computer, they will have the opportunity to electronically sign the eConsent via REDCap. The person obtaining consent will initiate the eConsent process from within REDCap for their name and a timestamp to appear on the study participant’s signed consent form. In order to authenticate that the person signing is that person, we will again use a passcode based on known information (e.g., the patient’s year of birth). Once the eConsent form is signed and submitted, the patient and/or legally

authorized representative will be able to receive a print out of the paper copy, download a pdf, and/or receive an email with a PDF attachment of the signed consent form.

7.3 The consent document

The informed consent document will provide consent for the entire study, though consent may be withdrawn at any time. Because this study includes only one "phase," we will not ask participants to re-consent during the study. The consent form will also contain information regarding HIPAA authorization, if participants consent to be contacted for future research studies, preferred method of contact (i.e., phone, text, email).

For individuals who are eligible and who provide informed consent, the following information will be entered into a secure electronic database (e.g., Excel on a password-protected computer). This information is needed in case contact is required after the study and/or the participant requires payment through the mail.

- Participant ID number (used to identify the participant on all study forms and notes)
- Name
- Participant phone number
- Participant home address
- Participant email address
- Medical Record number
- Date of informed consent
- Date of registration

If a person requests to waive or alter elements of the informed consent document, they will not be allowed to participate in the study. A note will be made in the screening log as to why written consent was not obtained. Similarly, if an individual requests to waive documentation of consent, they will not be allowed to participate. Study staff will reiterate that the only record linking the participant and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. If an individual waives or alters HIPAA Authorization, the person will also not be allowed to participate. Study staff will explain why the study cannot be conducted without the use or disclosure of protected health information (PHI), and describe the plan to protect identifiers from improper use and disclosure. It will also be explained that all forms will be held in a locked location for at least 6 years, and disposal of forms will occur in a confidential manner. PHI will not be reused or disclosed to any other person or entity except (i) as required by law, (ii) for authorized oversight of the research study, or (iii) for other research for which the use or disclosure of PHI would be permitted by the HIPAA Privacy Rule.

8. Study procedures

8.1 Overview of study

This study is a single-arm feasibility TRE intervention for 14 days, during which participants will be asked to consume all of their calories within a 10-h window. The primary goals are to assess the feasibility of implementing the intervention and participants' adherence to the dietary pattern over the 14 days. Information on fatigue and quality of life will also be collected; while large changes in these measures are not expected, it will be ensured that the diet pattern does not cause large amounts of fatigue, a large

reduction in quality of life, or exacerbation of any chronic symptoms. It is hypothesized that a longer duration intervention (e.g., at least 4-12 weeks[34]) will reduce cancer-related fatigue and other symptoms.

8.2 Study procedures, assessments, and participant activities

8.2.1 Screening procedures

Potential participants will be screened for their duration into survivorship (needs to be 4 months–5 years), age (needs to be ≥18 years old), and BMI (needs to be >20 kg/m^2). Potential participants also need to be in the habit of consuming food within a window that is larger than 10 hours and be experiencing fatigue (a score of 3 or higher on a scale of 0-10 for their worst fatigue in the last week). If there are any screen failures, we will retain the information in a screening log as described in §6.2 to avoid approaching them again.

8.2.2 Source of record or measures

The Clinical Record contains height, weight, current menopausal status, Karnofsky Performance Status or Eastern Cooperative Oncology Group (ECOG) Performance Status, comorbidities, cancer stage, surgical procedures, types and doses of treatments, and other clinical characteristics. The study team will use the medical record to complete as much of the Clinical Record as possible. The study team will also note all toxicity outcomes. All other questionnaires will be completed by the participant.

8.2.3 Research data in the medical record

Documentation of study participation will be included in the medical record by means of uploading a signed consent form to each participant's medical record, for those participants enrolled in the research study. No further research-related information will be included in the medical record.

The assessments will take place in one of two locations: 1) at the Wilmot Cancer Institute (including satellite locations) and 2) at home or participant's choice. The consent will take place at the clinic whenever possible, which comprises the Wilmot Cancer Institute, Pluta Cancer Center, or a Wilmot Cancer Institute-affiliated clinic, or can alternatively be accomplished remotely. The questionnaires will be completed electronically or on paper and can be completed at the clinic or at home (or wherever is convenient). Body weight data will be collected by the participant at their home using a portable bathroom scale that is provided by the study team. Therefore, this entire study can be completed remotely.

8.2.4 Duration of the study

Participants will participate in the study for approximately 3 weeks, including consent, baseline assessments, a 14-day intervention, post-intervention assessments, and an exit interview. After consent, each participant will need to complete a prospective, 24-h Food Record, after which the participant can begin the intervention. The participant can complete the Food Record, perform baseline assessments, and start the 14-day intervention any day within the first week of consent. However, the participant should begin the intervention within 3 days of completing baseline assessments and complete post-intervention assessments within 3 days of completing the intervention. The exit interview will be completed within 7 days of completing the intervention.

8.2.5 Schedule of assessments

After consenting to the study, the participant can decide to start the intervention any day within the next week. Preferably, the 24-h Food Record and baseline questionnaires will be performed the day before the intervention begins (Day 0) and body weight will be measured on the first day of the intervention (Day 1), but participants will be given up to 3 days to begin in case there are technical difficulties with REDCap or other barriers to starting the intervention. Similarly, it is preferred that post-intervention questionnaires are completed the day after the intervention ends (Day 15), but up to 3 days will be allowed. On Day 8, the participant will provide body weight. The Day 14 24-h Food Record should be performed on Day 14, but can be completed on Day 12, 13, or 14 if there are anticipated logistical reasons why completion of the diary on Day 14 would not be possible. Post-intervention exit interviews will be performed with a member of the study team within one week of completing the intervention. Participants will be asked to complete the daily diaries every day at the end of the day.

8.2.7 Data collection tables

A Clinical Record form will be completed by the study team using the medical record. These following table lists study-related activities that the participants will experience.

Assessment or Activity	Study Goal	Assessment Location	Baseline (approx. Day 0)	Inter-vention Day 1	Inter-vention (Day 1-14)	Inter-vention Day 8 (approx.)	Inter-vention Day 14 (approx.)	Post-intervention (approx. Day 15)
On-study data form	Demographics and clinical characteristics	Clinic or home (REDCap*)	✓					
24-h Food Record	Safety	Home	✓				✓	
Functional Assessment of Chronic Illness-Fatigue (FACIT-F)	Exploratory	Clinic or home (REDCap*)	✓					✓
Brief Fatigue Inventory (BFI)	Exploratory	Clinic or home (REDCap*)	✓					✓
Symptom inventory	Exploratory	Clinic or home (REDCap*)	✓					✓
Body weight	Safety	Clinic or home		✓		✓		✓
Daily diary	**Primary aim**	Home (REDCap*)			Every day, at the end of the day			
Check-in	Check-in	Remote				✓		
Exit interview	Exploratory	Clinic or home (telephone)						✓

*If a participant prefers, they may complete paper-based versions of these assessments and return them to the study team in-person or in a postage-paid envelope.

8.3 Plans for return of research results

All data collected as part of this study will be for research purposes only and participants will be explicitly told that the experiment will not provide information as to their health status.

9. Risks to participants

9.1 Risks to participants and adequacy of protection against risk

We will inquire about how the participant is feeling mid-way through the intervention and at the end.

9.1.1 Weight loss due to the intervention

Some studies have documented weight loss upon adoption of a TRE dietary pattern (10 hours of feeding/14 hours of fasting) despite consuming calories *ad libitum*.[9,35] This intervention diet will be *ad libitum* and participants will be encouraged to satisfy thirst and hunger. However, due to the time-restrictive nature of the TRE diet compared to the typical American eating patterns, there is a chance that patients could enter a calorie deficit and lose weight during the course of the intervention.[13] Minor weight loss will not be considered an adverse event (less than 3% in one week or 5% body weight in the 14 days). However, if a patient experiences rapid, unintentional weight loss, the participant will be encouraged to contact the medical monitor and their treating oncology team. The CTCAE, version 5,[2] will be used to report weight loss as an adverse event:

- Weight loss of 5% to less than 10% from baseline with no intervention indicated will be considered a Grade 1 adverse event.
- Weight loss of 10% to less than 20% from baseline and indicated nutritional support will be considered a Grade 2 adverse event.
- Weight loss greater than or equal to 20% from baseline with indicated tube feeding or total parental nutrition (TPN) will be considered a Grade 3 adverse event.

In order to closely monitor weight change, each participant will be provided with a scale to use at home. Due to the short nature of this intervention (i.e., 2 weeks), no adverse events due to weight loss are anticipated. However, in the event that this occurs, the treatment team's recommendations for nutritional interventions due to any weight loss will be followed.

Weight loss can cause anxiety in cancer survivors who might think that their cancer is recurring. However, knowing that this dietary intervention often results in weight loss, particularly in people who are overweight,[17] can be reassuring in that weight loss is due to dietary change and not a manifestation of progressive cancer, particularly if there are no other concerning symptoms.

As always, the patient has the right to eat or drink outside of the 10-h window, and to withdraw from the study at any time.

Probability: Moderate probability that some weight loss will be experienced, especially in patients with excess body fat; very low probability that a dangerous amount of weight will be lost

Magnitude: Low

Duration: Short- to long-term

9.1.2 Hunger and hunger-related symptoms due to the intervention

For most participants, eating within only a 10-h window will mean re-adjusting their typical eating pattern. Many participants will need to rearrange their meal times—either delay breakfast or eat dinner earlier. If they delay breakfast, they might feel hungry in the few hours leading up to their eating window, especially in the first few days of the study. Similarly, they might crave something before bed if they are in the habit of eating before bed. With hunger can come lack of concentration, fatigue, dizziness, irritability, and other symptoms. All participants will be encouraged to stay hydrated and to consume a snack outside of the window if symptoms become debilitating.

Probability: Moderate

Magnitude: Low to moderate

Duration: Short-term

9.1.3 Emotional distress due to the intervention or the outcome measures

There is a chance that participants could become emotionally distressed by the expectation to consume food only in the 10-h window. Each participant will be reassured that deviations from the plan are permitted, especially if they are feeling sluggish, dizzy, or sick.

These questionnaires contain information that might be distressing or private (e.g., "I am satisfied with family communication about my illness" from the FACIT-F). Participants will be reminded that they do not have to answer any questions they are not comfortable answering, and they can take a break or stop answering the questionnaires at any time.

Probability: Low

Magnitude: Low

Duration: Short-term

9.1.4. Breach of confidentiality

There is always a risk of a breach of confidentiality in which sensitive medical information could become known to persons outside the research team. To avoid leakage of sensitive information, only Dr. Kleckner (the study chair) and any individual designees will have access to the screening log and the file that links participant name with participant number (both will be encrypted); these files will be stored on a password-protected computer in her private office in the Cancer Control Unit in Saunders Research Building. All data files will reference participants by a non-identifiable Participant ID and will be stored on Dr. Kleckner's computer and secure servers at URMC. All consent forms will be stored in a locked cabinet also in her office. If Dr. Kleckner shares data with any other researcher for analyses, all data will be deidentified (i.e., void of name, birthdate, and contact information). Presentation of data in the form of posters, presentations, grant applications, and manuscripts, either in private or public settings, will not have any identifiable information. Dr. Kleckner and all other co-investigators participate in ethical training in accordance with URMC policies (e.g., online coursework via the CITI collaborative).

Probability: Very low

Magnitude: Low to high

Duration: Unknown

9.1.5 Risk to groups or society

There are no known risks to groups or societies.

9.2 Alternatives to participation

The patient can seek other nutritional services in addition to or instead of participating in this study. The participant may choose to not participate in the study without penalty or effects on medical care.

10. Potential benefits to participants

Participants may or may not directly benefit from this study. Participants will be encouraged to consume a new dietary pattern that has been shown to improve health, and will likely make them more aware of the composition of their diet as well as their eating habits. It is hypothesized that the diet pattern will have a positive effect on their symptoms, though it may not.

11. Costs for participation

There will be no costs to the participants or the participants' insurance for assessments, screening tests, instruments/equipment, or parking. The participants will be responsible for travel to and from the research site.

12. Payment for participation

Participants will receive payments of $10 to complete pre-intervention measures, $10 to complete daily diaries (at least 10/14 days), and $10 to complete post-intervention measures for a total of $30. They will also be able to keep the portable scale.

13. Participant withdrawals

Participants may discontinue participation in the study at any time if they do not wish to take part any longer. Participants may be withdrawn from the study by research personnel if it is deemed in their best interest to no longer participate or in the case of lack of cooperation, non-compliance, or other administrative reasons. In the event that a participant does withdraw from the study, the information they have already provided will be kept in a confidential manner. A 10-20% withdraw rate is built into the study design and recruitment goal, so there should not be a need to replace participants who withdraw before completing the study. For participants who do not complete study, available data will be utilized during the analysis.

14. Privacy and confidentiality of participants and research data

14.1 Steps taken to protect privacy

14.1.1 Assignment of Participant Identification (ID) number

The study team will assign a numerical Participant ID to each participant once they have signed the consent form (e.g., 101, 102, etc.). Notes and databases will use this number and the participant's first and last initials as identifiers to ensure data integrity. Other identifying information will not exist on these forms. A complete list of study participants with Participant ID, name, and contact information will be maintained separately for the purpose of contacting participants if necessary; this database will be maintained for at least six years after the study is complete. This linkage information will be maintained and only accessible to Dr. Kleckner, the study chair, who will provide individuals with private access only if necessary. All data files will reference participants by the Participant ID and will be stored on Dr. Kleckner's computer and secure servers at URMC. All consent forms will be stored in a locked cabinet also in her office. If Dr. Kleckner shares data with any other researcher for analyses, all data will be deidentified (i.e., void of name, initials, birthdate, and contact information). Presentation of data in the form of posters, presentations, grant applications, and manuscripts, either in private or public settings, will not have any identifiable information.

14.1.2 Assessments performed in discrete locations

Face-to-face consent and other study activities will be performed in a private room, usually where their oncology appointments typically take place (e.g., Wilmot Cancer Institute, Pluta Cancer Center).

14.1.3 Audio-recorded interviews

All audio-recorded interviews will be transferred to Dr. Kleckner's secure computer and server at URMC within 72 hours of the interview and then immediately deleted from the recorder. All interview file names will not include the participant's name or any identifying information.

14.2 Study teams' access to participant information

Electronic medical records will be used to screen patients. Only those with proper training will have access to this database and medical records.

All data will be collected electronically using REDCap software (unless a participant prefers paper copies, in which case their data will be transferred to REDCap). REDCap is a secure, web-based application for building and managing online surveys and databases and is made available through the CTSI. Study data in REDCap will only by accessed by members of the study team.

Paper forms, if available, will be labeled with Participant ID and participant initials and not identifiable information. Only members of the study team or those analyzing the data will have access to these.

All data will be compiled into several databases that will identify participants by Participant ID and *not* name, initials, or contact information. If data are shared in the future with other researchers (e.g., a trainee), only databases without identifiable information will be shared and access will only be given to that specific individual.

14.3 Contacting participants

This is a 14-day intervention study, and participants will be contacted throughout the study period. Participants will be contacted approximately half-way through (Day 5-12, preferably Day 8) to ask how the dietary intervention is going, how the daily diaries are going, and to ensure they acquired the body weight measurement (or remind them to measure body weight) at Day 8. For these contacts, we will ask if phone, text, or email is preferred. REDCap software also contacts participants with reminders to complete questionnaires.

Two-way text messaging will occur using Dr. Kleckner's personal mobile device using a Google Voice phone number. We expect that messages will be seldom, and include correspondence such as this:

- I know we were supposed to meet at 1pm tomorrow, but something came up. Can we do 2pm instead?
- Am I allowed to drink chamomile tea outside my eating window as long as I don't add sugar?

We will provide appointment reminders via text, phone, or email based on participants' preferences as indicated on the consent form. We will not require a response to confirm the appointment, and participants can opt out of any future text messaging by sending a message such as "Stop Research Text." We will not provide or ask for any personal health information via text message or email.

14.4 Data confidentiality, storage, and sharing

Paper-based data will be stored in a locked cabinet in Dr. Kleckner's office in the Cancer Control division of URMC in Saunders Research Building. Electronic data will be stored on Dr. Kleckner's desktop computer in her office in Saunders research building. The Cancer Control Unit is an office suite secured by electronic key cards; Dr. Kleckner's personal office is secured by a traditional key; Dr. Kleckner's file cabinet is secured by a unique traditional key; and Dr. Kleckner's computer is password-protected. Electronic research records are stored on URMC's password-secured and firewall-protected networks. These are the same methods of security used for patient medical records. In the rare case that any data are transferred outside of the University, only deidentified databases will be shared with approved individuals for private access. Databases will be transferred through URMC's HIPAA-compliant box.com under the direction of Dr. Kleckner or a designee, with oversight by the Cancer Control Information Technology staff. It is anticipated that data will only be shared for research purposes only, but it is possible that data could be used for teaching or other purposes. To reiterate, <u>all shared data will be deidentified</u>.

Only members of the study team will have access to the stored data. All individuals who have access to the data will need to complete human participant training as required by URMC. Participants' individual research records will not be shared with their treating physician unless they provide consent or the participant's treating physician is Dr. Richard Dunne, in which case he will have access to study data as a study co-investigator. Overall study results may be presented to participants, faculty, and staff at URMC after completion of the study. Study results will be presented at professional meetings, published, and reported on clinicaltrials.gov (NCT04243512).

All study data will be kept for at least six years after the study and all reports and publications are complete.

15. Data/sample storage for future use

All data collected for the current study will be used in post-hoc analyses as appropriate. These analyses could provide preliminary data for future studies. Data will be stored long-term as described in §14.4. Any individual who would like access to deidentified raw data must submit a request to the study chair (i.e., Dr. Amber Kleckner) via a written request (e.g., email). If Dr. Kleckner considers the project appropriate, she will approve a release of the data and transfer it in a safe, HIPAA-compliant manner as described in §14.4.

16. Data analysis and monitoring

The James P. Wilmot Cancer Institute Data Safety Monitoring Committee (DSMC) will serve as the DSMC of record for this study. The DSMC provides oversight of study progress and safety by review of accrual and events at regularly scheduled meetings. The frequency of review is determined by the size, risk, and complexity of the trial.

Dr. Kleckner, the study chair, will conduct continuous review of data and participant safety. The Investigator will submit annual progress reports of these data to the DSMC for review. The review will include the number of participants enrolled, withdrawals, and adverse events (both expected and unexpected). A copy of the Adverse Event spreadsheet along with the Progress Report will be submitted to the DSMC for review. Actual review dates will be assigned when the first participant is accrued.

Any adverse event that is serious, related, and unexpected will be reported within 10 calendar days to both the Safety Coordinator (e.g., Sarah Strause) and the RSRB. The DSMC Chair will determine whether further action is required, and when participant safety is of concern. When participant safety is of concern, an interim meeting may be called.

Serious adverse events that are related and expected or unrelated and unexpected will be reported to the Committee for review at the quarterly meeting. Serious adverse event reports will include sufficient detail so that the DSMC can determine the severity, toxicity grade, expectedness, treatment required, and a follow-up report documenting resolution of if there are sequelae. Serious adverse events that require detailed reports (but not necessarily expedited) are expected, related, non-hematologic toxicities of grade 3, 4 or 5.

17. Data analysis plan

17.1 Sample size determination

This is a single-arm feasibility pilot study that will assess the feasibility of recruiting cancer survivors to a TRE intervention trial and their adherence to the diet pattern for two weeks. The goal is to assess feasibility of recruitment and retention so that these data can be used in a follow-on grant application in mid-2020; this larger study will be used to obtain preliminary efficacy data for TRE on cancer-related fatigue. It is common that single-arm pilot studies implementing dietary interventions recruit 10-40 participants (e.g., TRE study among overweight older adults, n=10;[36] ketogenic diet among patients with recurrent glioblastoma, n=20;[37] lifestyle intervention including diet among overweight breast cancer survivors, n=14[38]). In total, 40 participants will be recruited, and approximately 20% attrition is anticipated, providing evaluable data from approximately 32 participants.

17.2 Statistical analysis

The primary objective of this study is to assess the feasibility of delivering a TRE intervention to cancer survivors by way of adherence. As the primary endpoint, we will determine how many days the participants were able to restrict their eating to the 10-h window. Success will be deemed if participants on average reach the fasting target at least 11 of the 14 days (79% of days). This goal is based on prior TRE studies.[17,21] A secondary aim is retention; it is hypothesized that at least 80% (32 out of 40) of those who provide baseline data also provide post-intervention data; this goal is based on prior studies conducted by the Division of Cancer Control.

To ensure safety of this intervention, body weight will be monitored weekly from baseline to post-intervention. It is anticipated that no one will lose more than 3% body weight in one week or 5% body weight over the 14 days.

In exploratory analyses, we will assess fatigue and well-being from the FACIT-F and BFI questionnaires, as well as general symptoms from the Symptom Inventory. The distribution of the outcome measures at baseline, at 14 days, and the change score (from baseline to 14 days) will be first assessed visually (e.g., histogram) and then descriptive statistics [e.g., range, interquartile range, mean (95% confidence interval), standard deviation] will be evaluated. The magnitude of the change score together with variability and distribution data will be used to inform the sample size and design of our future study. A paired t-test will be used to formally assess whether the change over time was different from zero with a two-tailed α of 0.10. For a particular outcome measure, n=32 patients provides 80% power to detect changes at the magnitude of 0.45 of the measured variability estimated by the standard deviation.

17.3 Quality control

Electronic forms will be used and our database will be audited by standard URMC procedures. All data will be visually inspected. For exploratory measures, if distributional assumptions are not met (e.g., normality of residuals), transformations or nonparametric methods will be used. Outliers will be closely examined to determine if they are erroneous; if they are valid, sensitivity analyses (with and without outliers) will be used. Hypothesis testing will use α=0.10 (two-tailed). The study team will work closely with Dr. Eva Culakova and her team (e.g., Dr. Huiwen Xu, Mr. Javier Bautista)—biostatisticians in the Division of Cancer Control.

17.4 Missing data

REDCap allows data entry forms to facilitate completion of all measures.[39] The reasons for missing data will be tabulated. Under the missing at random (MAR) assumption, multiple imputation will be used to obtain unbiased estimates of key statistics. If data are suspected to be missing not at random (MNAR), we will perform a sensitivity analysis using pattern mixture models.

10. References

1. National Cancer Institute: Notice of Intent to Publish a Funding Opportunity Announcement for Research Answers to NCI's Provocative Questions, 2019
2. U.S. Department of Health and Human Services: Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, 2017

3. Berger AM, Mooney K, Alvarez-Perez A, et al: Cancer-Related Fatigue, Version 2.2015, Clinical Practice Guidelines in Oncology. Nat Comp Cancer Netw 13:1012-1039, 2015
4. Servaes P, Verhagen C, Bleijenberg G: Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. European Journal of Cancer 38:27-43, 2002
5. Saligan LN, Olson K, Filler K, et al: The biology of cancer-related fatigue: a review of the literature. Support Care Cancer 23:2461-78, 2015
6. Abbott SM, Malkani RG, Zee PC: Circadian disruption and human health: A bidirectional relationship. Eur J Neurosci, 2018
7. Payne JK: Altered circadian rhythms and cancer-related fatigue outcomes. Integr Cancer Ther 10:221-33, 2011
8. Roscoe JA, Morrow GR, Hickok JT, et al: Temporal interrelationships among fatigue, circadian rhythm and depression in breast cancer patients undergoing chemotherapy treatment. Support Care Cancer 10:329-36, 2002
9. Wilkinson MJ, Manoogian ENC, Zadourian A, et al: Ten-Hour Time-Restricted Eating Reduces Weight, Blood Pressure, and Atherogenic Lipids in Patients with Metabolic Syndrome. Cell Metab, 2019
10. Forbes-Robertson S, Dudley E, Vadgama P, et al: Circadian disruption and remedial interventions. Sports Med 42:185-208, 2012
11. Mustian KM, Sprod L, Peppone LJ, et al: Effect of YOCAS yoga on circadian rhythm, anxiety, and mood: A URCC CCOP randomized, controlled clinical trial among 410 cancer survivors., ASCO Annual Meeting. Chicago, IL, Journal of Clinical Oncology 2011, pp 9034
12. Zarrinpar A, Chaix A, Panda S: Daily Eating Patterns and Their Impact on Health and Disease. Trends Endocrinol Metab 27:69-83, 2016
13. Gill S, Panda S: A Smartphone App Reveals Erratic Diurnal Eating Patterns in Humans that Can Be Modulated for Health Benefits. Cell Metab 22:789-98, 2015
14. Chaix A, Manoogian ENC, Melkani GC, et al: Time-Restricted Eating to Prevent and Manage Chronic Metabolic Diseases. Annu Rev Nutr 39:291-315, 2019
15. Melkani GC, Panda S: Time-restricted feeding for prevention and treatment of cardiometabolic disorders. J Physiol 595:3691-3700, 2017
16. Hatori M, Vollmers C, Zarrinpar A, et al: Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. Cell Metab 15:848-60, 2012
17. Gabel K, Hoddy KK, Haggerty N, et al: Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: A pilot study. Nutr Healthy Aging 4:345-353, 2018
18. Jamshed H, Beyl RA, Della Manna DL, et al: Early Time-Restricted Feeding Improves 24-Hour Glucose Levels and Affects Markers of the Circadian Clock, Aging, and Autophagy in Humans. Nutrients 11, 2019
19. Oishi K, Higo-Yamamoto S, Yasumoto Y: Moderately high doses of the artificial sweetener saccharin potentially induce sleep disorders in mice. Nutrition 32:1159-61, 2016
20. Burke T, Markwald RR, McHill AW, et al: Effects of caffeine on the human circadian clock in vivo and in vitro. Science Translational Medicine 7:305ra146, 2015
21. Kesztyus D, Cermak P, Gulich M, et al: Adherence to Time-Restricted Feeding and Impact on Abdominal Obesity in Primary Care Patients: Results of a Pilot Study in a Pre-Post Design. Nutrients 11, 2019
22. Cella D: The Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale: A new tool for the assessment of outcomes in cancer anemia and fatigue. Seminars in Hematology 34:13-19, 1997

23. Mendoza TR, Wang XS, Cleeland CS, et al: The Rapid Assessment of Fatigue Severity in Cancer Patients. Cancer 85:86-96, 1999

24. Cleeland CS, Mendoza TR, Wang XS, et al: Assessing Symptom Distress in Cancer Patients. Cancer 89:1634-1646, 2000

25. Dodd MJ, Cho MH, Cooper BA, et al: The effect of symptom clusters on functional status and quality of life in women with breast cancer. Eur J Oncol Nurs 14:101-10, 2010

26. Stekovic S, Hofer SJ, Tripolt N, et al: Alternate Day Fasting Improves Physiological and Molecular Markers of Aging in Healthy, Non-obese Humans. Cell Metab 30:462-476 e5, 2019

27. Tinsley G, Forsse JS, Butler NK, et al: Time-restricted feeding in young men performing resistance training: A randomized controlled trial. European Journal of Sport Science 17:200-207, 2017

28. McMillan L, Owen L, Kras M, et al: Behavioural effects of a 10-day Mediterranean diet. Results from a pilot study evaluating mood and cognitive performance. Appetite 56:143-7, 2011

29. Beshyah SA, Hassanein M, Ahmedani MY, et al: Diabetic hypoglycaemia during Ramadan fasting: A trans-national observational real-world study. Diabetes Res Clin Pract 150:315-321, 2019

30. Singh RB, Takahashi T, Hristova K, et al: Effects of Circadian-Restricted Feeding and Low Energy Intake, On Risk of Cardiovascular Disease and Type 2 Diabetes Mellitus. World Heart Journal 8:315-327, 2016

31. Arnason TG, Bowen MW, Mansell KD: Effects of intermittent fasting on health markers in those with type 2 diabetes: A pilot study. World Journal of Diabetes 8:154-164, 2017

32. Sutton EF, Beyl R, Early KS, et al: Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. Cell Metab 27:1212-1221 e3, 2018

33. Esposito S, Tenconi R, Preti V, et al: Chemotherapy against cancer during pregnancy: A systematic review on neonatal outcomes. Medicine (Baltimore) 95:e4899, 2016

34. Lin PJ, Kleckner IR, Loh KP, et al: Influence of Yoga on Cancer-Related Fatigue and on Mediational Relationships Between Changes in Sleep and Cancer-Related Fatigue: A Nationwide, Multicenter Randomized Controlled Trial of Yoga in Cancer Survivors. Integr Cancer Ther 18:1534735419855134, 2019

35. LeCheminant JD, Christenson E, Bailey BW, et al: Restricting night-time eating reduces daily energy intake in healthy young men: a short-term cross-over study. Br J Nutr 110:2108-13, 2013

36. Anton SD, Lee SA, Donahoo WT, et al: The Effects of Time Restricted Feeding on Overweight, Older Adults: A Pilot Study. Nutrients 11, 2019

37. Rieger J, Bahr O, Maurer GD, et al: ERGO: a pilot study of ketogenic diet in recurrent glioblastoma. Int J Oncol 44:1843-52, 2014

38. Campbell KL, Van Patten CL, Neil SE, et al: Feasibility of a lifestyle intervention on body weight and serum biomarkers in breast cancer survivors with overweight and obesity. J Acad Nutr Diet 112:559-67, 2012

39. Wisniewski SR, Leon AC, Otto MW, et al: Prevention of missing data in clinical research studies. Biol Psychiatry 59:997-1000, 2006