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TIME RESTRICTED EATING FOR WEIGHT LOSS MAINTENANCE (TWIST): A SINGLE-SITE, PILOT FEASIBLITY AND ACCEPTABLITY RANDOMIZED CLINICAL TRIAL IN ADULTS WITH RECENT WEIGHT LOSS

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NYULMC Study Number:	i22-01453
Funding Sponsor:	NIH NHLBI 31 Center Dr, Bethesda, MD 20892 (301) 592-8573
ClinicalTrials.gov Number	Pending

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Statement of Compliance
This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

AE	Adverse Event/Adverse Experience
AOM	Anti-Obesity Medications
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
mCC	myCircadianClock
N	Number (typically refers to participants)
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
TRE	Time Restricted Eating
US	United States

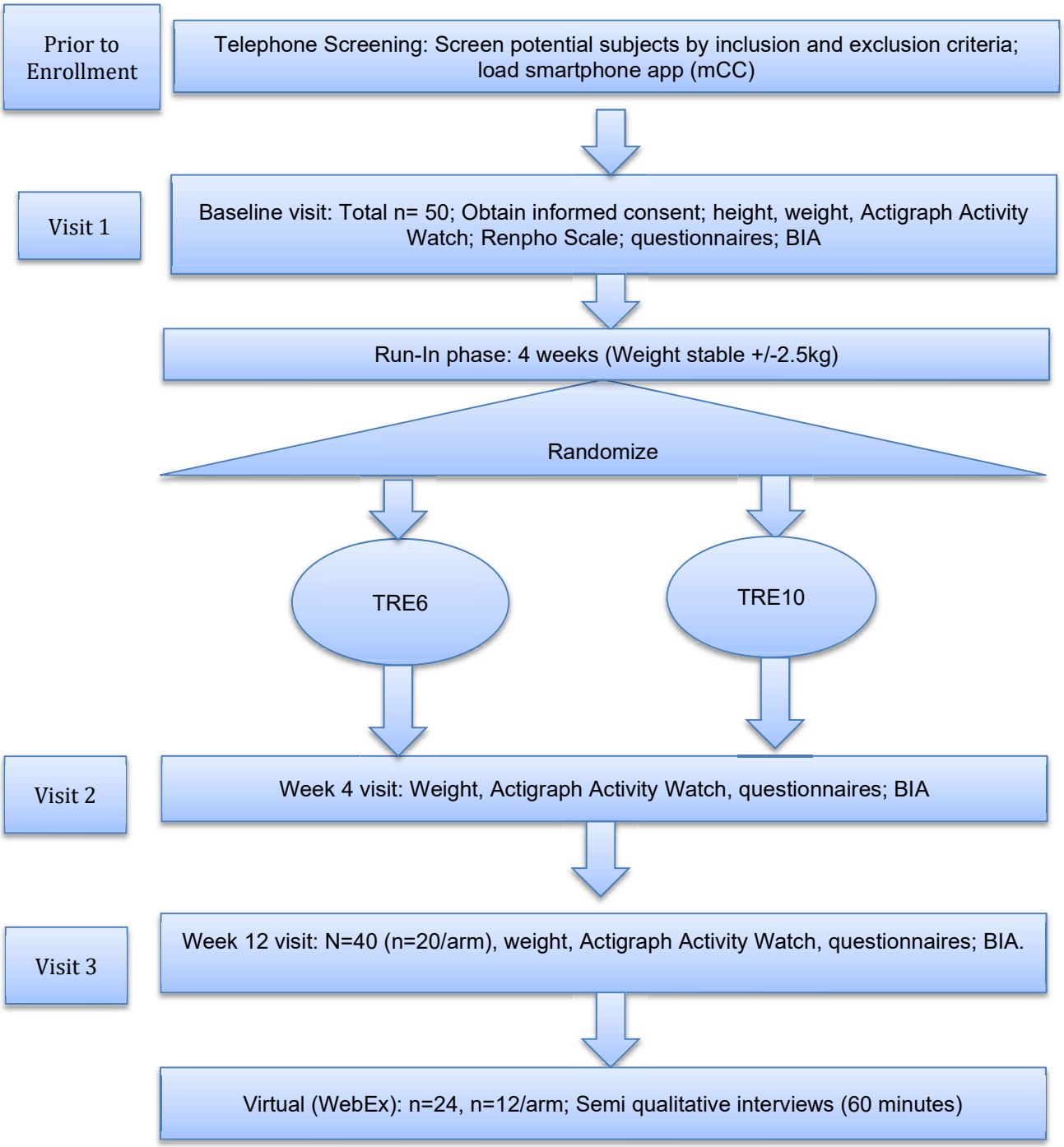
WLM	Weight Loss maintenance

Protocol Summary

Title	Time restricted eating for weight loss maintenance: A single-site, pilot feasibility and acceptability randomized clinical trial in adults with recent weight loss
Short Title	A pilot study of time restricted eating for weight loss maintenance
Brief Summary	The aim of this pilot feasibility and acceptability, randomized clinical trial will be to examine the effects of two-time restricted eating (TRE) interventions on weight loss maintenance (WLM). This study will be conducted in 40 overweight or obese individuals with non-surgical weight loss of ≥5% initial body weight recruited from the NYU Langone Health Weight Management Program and NY-MOVE! Weight Management Clinic at the Manhattan VA. Measurements will occur at baseline, 4 and 12 weeks. Participants will be randomized with equal allocation to 2 groups: (1) TRE6 or (2) TRE10. The TRE6 will restrict their eating window to 6 hours per day and the TRE10 to 10 hours per day.
Phase	1
Objectives	**Primary objective:** To determine the feasibility and acceptability in terms of recruitment, retention, and intervention adherence to TRE10 and TRE6 after 12 weeks using a mixed methods design. **Secondary Aim 1:** To determine individual, family and neighborhood/community level barriers and facilitators to each TRE intervention such as motivation, cultural factors, occupation, and family structure. **Exploratory Aim:** To describe the changes in lean mass and fat mass in each TRE intervention.
Methodology	Single-phase, parallel arm, 2 group randomized clinical trial
Endpoint	Primary endpoint 1.1: recruitment and retention at 12 weeks Primary endpoint 1.2: Acceptability of participant experience using TRE Experience questionnaire (TRE-EQ) and semi-structured, qualitative interviews Primary endpoint 1.3: Adherence to the eating window Secondary Aim: Barriers facilitators to each TRE intervention Exploratory: body fat and lean mass using BIA
Study Duration	15 months
Participant Duration	Total Time: 4 months
Population	N=40; males and females, 25-65 years; recent weight loss (≥5% initial body weight); BMI >20.5 kg/m^2
Study Sites	NYU Langone Health; 180 Madison Ave
Number of participants	50 participants projected
Description of Study Agent/Procedure	TRE intervention that restricts the eating window
Reference Therapy	No reference therapy
Key Procedures	Height, weight, semi-structured qualitative interviews; BIA

Statistical Analysis	**Quantitative data analysis:** A descriptive analysis of all data collected at each time point will be performed on measures of feasibility, acceptability and eating window adherence using appropriate graphical and numerical exploratory data techniques. Logistic regression will be used to explore predictors of TRE intervention eating window adherence. Linear regression models predicting reduction in the eating window and adherence from the patient experience will be run separately for data obtained from the acceptability and feasibility of intervention scores at 2 weeks and 12 weeks. **Mixed Methods.** In a sequential explanatory design, the quantitative data (eating window adherence, TRE-EQ) will be analyzed and used to build the qualitative interviews. We will purposefully select participants with lowest and highest eating window adherence from each arm in order to develop context and a deeper understanding of barriers and facilitators, respectively. The qualitative interviews will be analyzed using thematic analysis. We will integrate qualitative data and visualize it in combination with the quantitative data using a matrix analysis technique.

Schematic of Study Design



1 Key Roles

Mary Ann Sevick, ScD (Principal Investigator (past))
Department of Population Health
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180 Madison Avenue, New York, NY 10016 646-501-3427
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Dr. Sevick is a Professor in the Department of Population Health in the School of Medicine at New York University, and Director of the mHealth Unit. Over the past 25 years, Dr. Sevick has had experience with a variety of large clinical trials involving behavior change strategies including the Women's Health Initiative, the Activity Counseling Trial; the Arthritis, Diet & Activity Promotion Trial; the Reconditioning & Exercise for COPD Trial; and Applications for Lifestyle Exercise study. Her primary interest is in the area of chronic illness and she has recently been involved, as Principal Investigator, in several studies to examine adherence to disease management regimens. Dr. Sevick was the PI on the AHA-funded Personal Diet Study (17SFRM33590133), a personalized technology-supported weight loss intervention targeting post-prandial glycemic response in adults with overweight and obesity, and a recently initiated R01 entitled Precision Nutrition for Diabetes Management (R01NR018916) that will use the same methods as the Personal Diet Study, but targeting glycemia management in adults with early-stage type 2 diabetes. These studies uniquely prepare her to conduct the proposed study. Dr. Sevick has extensive experience implementing clinical interventions that employ technology in clinical populations. She will serve as Dr. Popp's mentor and maintain weekly project meetings helping to oversee Recruitment, Measurement, Intervention, Data Management and Analysis Subcommittees.

Collin Popp, PhD, MS, RD (Principal Investigator (current))
Institute for Excellence in Health Equity
Department of Population Health; NYU Grossman School of Medicine
180 Madison Avenue New York, NY 10016
(646) 501-3446

Dr. Popp is an early-stage investigator in the Department of Population Heath. He has extensive experience in nutrition, exercise physiology and weight management. He served as post-doc on the Personal Diet study with Dr. Sevick (17SFRM33590133) and currently serves as a co-Investigator on Dr. Sevick's Precision Nutrition for Diabetes Management (R01NR018916). He will head the Recruitment, Measurement, Intervention, Data Management and Analysis Subcommittees.

Holly Lofton, MD (Co-Investigator)
Department of Surgery and Department of Medicine
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Dr. Lofton is a Clinical Associate Professor in the Departments of Surgery and Medicine in the School of Medicine at New York University. She currently serves as Director of the NYU Langone Health Medical Weight Management Program (NYULH-WMP), and is the Program Director of the Clinical Obesity Medicine Fellowship. The NYULH-WMP supports over 3000 patients with weight loss options, including the New You program, a 12-week weight loss program that combines meal replacements and nutritional counseling offered as routine care through the NYU-MWMP. Dr. Lofton will guide the investigative team in developing the recruitment strategy.

Margaret Curran, MS (Program Manager)
Institute for Excellence in Health Equity
Department of Population Health; NYU Grossman School of Medicine
180 Madison Avenue New York, NY 10016

Ms. Curran is a Program Manager in the Department of Population Health. She has extensive experience in the implementation, development, and management of clinical trials. This includes recruitment and basic administrative

duties during the lifecycle of a clinical trial. She will assist Dr. Popp with recruitment and enrollment activities, and data management.

Sarah Moore, MD (Sub-Investigator)
NYU Langone Health
462 1st Ave, New York, NY 10016
Sarah.Moore@nyulangone.org

Dr. Moore is a Clinical Associate Professor in the Department of Medicine at NYU Langone Health. She sees patients at Bellevue Hospital for obesity and diabetes treatment. On average, she sees 20-30 patients per month in a primary care setting. Dr. Moore will guide the investigative team in developing a recruitment funnel from Bellevue hospital.

Sonya Henry (Research Data Associate)
Institute for Excellence in Health Equity
Department of Population Health; NYU Grossman School of Medicine
180 Madison Avenue New York, NY 10016
Sonya.Henry@nyulangone.org

Ms. Henry is a Research Data Associate (RDA) in the Department of Population Health. She will play a crucial role in ensuring the accuracy, integrity, and organization of all research-related data. Responsibilities will encompass comprehensive data collection, including patient demographics and medical history, treatment interventions, and clinical outcomes. Ms. Henry will meticulously input and manage data in compliance with established protocols and regulatory guidelines, performing routine quality checks to identify and rectify discrepancies. Additionally, the role involves collaborating closely with the research team to generate regular reports, maintain a secure data storage system, and facilitate data audits to guarantee the trial's reliability and validity. She will work with Drs. Popp and Sevick to recruit and enroll patients from the clinics of Drs. Lofton, Figueredo-Dietes and Moore.

Department of Population Health (DPH), NYU School of Medicine: DPH aims to integrate, support, and advance NYULH's contributions to population health research and related disciplines, providing a vibrant departmental home for the "bedside-to- population" as well as the "population-to-discovery" domains of translational research. It provides an academic base for efforts to integrate research into NYU's expanding health care delivery system that transcends any particular school, department, or division. DPH is a research and training hub that brings together researchers in nursing, medicine, psychology, epidemiology, biostatistics, health services and policy, behavior change, comparative effectiveness, medical ethics, prevention, and related disciplines, affording a unique and collaborative environment focused on improving the health of populations. The Department was initiated in January 2012. A core focus of DPH is improving health outcomes through innovative interventions as well as in enhancing the impact of interventions already known to be effective through implementation and dissemination. Collaboration with key public sector stakeholders and with community partners is central to the Department's mission. As researchers, faculty are engaged in dual roles: building cutting-edge science in their areas of inquiry, and providing collaborative consultation to other investigators throughout the NYULH academic community as well as across the University. Resources within the Department for this proposal include the use of dedicated office space located on the 7th floor at 180 Madison Avenue in New York City, telecom (phone, fax and LAN connections), administrative assistants, and grant, regulatory (IRB) and finance administrators.

Center for Healthful Behavior Change, NYULMC: The Center for Healthful Behavior Change (CHBC) is located within the Department of Population Health. The mission of CHBC is to become a national leader in translational behavioral medicine, research, training, and education. The CHBC works toward this mission through the development, implementation, and dissemination of innovative evidence-based behavioral interventions in routine clinical practice and community-based settings with the long-term goal of disseminating effective strategies nationally and internationally. The Center is comprised of core research faculty members with expertise in various fields relevant to translational behavioral research. Faculty engage in research pertaining to heart disease, hypertension, chronic kidney disease, diabetes, cancer, health disparities research, community-based participatory research, health psychology, behavioral informatics, and health education and counseling.

Weight Management Program at NYULH (NYULH-WMP; Director: Holly Lofton, MD): The Weight Management Program at NYULH is located at Tisch Hospital. The program is highly regarded, with experts in medical and surgical weight loss that includes gastric sleeve, LAP-BAND®, gastric balloon, and gastric bypass. Accredited by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP), NYULH-WMP is a comprehensive center providing high-quality, patient-centered care for both adults and adolescents. The medical weight loss option is coordinated by Dr. Holly Lofton MD, who specializes in medically supervised weight loss. There is a 3-mo or 6-mo option for patients based on the *New You* program, a standard of care weight loss program that employs a low-carbohydrate, ketogenic diet of approximately 1,080 kcal/day. The daily dietary regimen consists of three Robard medical grade, high-protein, low-carbohydrate liquid meal replacements, a 160-calorie protein bar, and a 350-calorie, self-prepared meal/day. Patients are instructed not to consume additional calories from fat, liquids, condiments, or other sources. Patients are provided written and verbal dietary instructions at their first visit, access to biweekly in-person support groups, and email and phone interaction with a physician and dietitians. Patients are also instructed to engage in 240 minutes of walking per week.

New York MOVE! Weight Management Program (Director: Dr. José Alemán MD, PhD): The MOVE! Weight management program is a Veteran's Affairs (VA) National Center for Health Promotion and Disease Prevention (NCP). MOVE! is an evidence-based self-management program that focuses on health and wellness through healthy eating, physical activity, and behavior change. Started in 2017, this clinic augments lifestyle intervention through the MOVE! program with meal replacement or pharmacotherapy within the spectrum of care for veterans with obesity and relevant comorbidities.

Division of Biostatistics NYULMC: Dr. Li's office is in the Division of Biostatistics, Department of Population Health, NYU School of Medicine at 650 First Avenue, a short walk from Drs. Sevick and Popp's office. Dr. Li has access to state-of-the-art computing facilities that include a central server (Dell PowerEdge 2500) and a Sun Server. Statistical software available either on the network or the desktop includes SAS, SPSS, S-Plus (including Spatial Stats and Environmental Statistics Modules), R, PASS and Matlab.

2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Obesity trends may be the result of failure to sustain WLM. Data from the National Health and Nutrition Examination Survey indicate that two-thirds of adults with obesity report "attempting to lose weight" in the previous year.[1] Surprisingly, ~60% are successful at losing 5–10% of their body weight. A 5% reduction in body weight significantly reduces the metabolic risk associated with adiposity-based chronic diseases.[2] Despite short-term weight loss success (3–6 mos) the majority of individuals fail to sustain long-term WLM.[3,4] Of those adults with obesity who are successful at weight loss, 80% are unable to maintain a >10% weight loss at one year.[1] Over one-third of adults regain body weight within a year, and nearly all regain within 5 years after weight loss.[5,6]

Weight loss results in a dynamic, physiological pressure to restore and regain body weight. According to the energy gap concept, failure to sustain WLM may result from an increase in hunger and a reduction in energy expenditure, resulting in a gap between energy desired and energy required.[7,8] The decrease in body mass, namely fat-free mass, results in a concomitant decrease in resting energy expenditure.[9,10] This is accompanied by parallel changes in appetite-associated hormones. Diet-induced weight loss elevates the hunger-associated hormones ghrelin and gastric inhibitory polypeptide[11,12] and decreases satiety-associated hormones, namely leptin, peptide YY (PYY), and glucagon-like peptide-1 (GLP-1).[11,13–15] Furthermore, subjective feelings of hunger, desire to eat, fullness, and appetite occur as result of weight loss.[11,16] Together, the changes in both subjective appetite and appetite hormones following weight loss are considered the main drivers of weight regain, although the mechanisms surrounding this evidence are speculative.[11,17]

"Closing" the energy gap with time-restricted eating (TRE). In theory, "closing" the energy gap can be achieved with bio-behavioral strategies that either increase energy expenditure (e.g., physical activity) or reduce hunger (e.g., meal timing). An untested strategy for reducing hunger is TRE, a form of intermittent fasting in which daily caloric intake is consumed with a predetermined eating window of 4–10 h/day. TRE requires little education or knowledge on behalf of the user, and there is no deliberate caloric restriction. Studies in animal models show a wide range of metabolic benefits[18–22], although the evidence is limited, but growing, in humans.[23–25] TRE has a particularly

interesting effect on appetite regulation. Improvements in morning hunger and evening satiety have been observed after only four days of TRE (6 h eating period) versus a control (12 h eating period).[26] TRE also reduces appetite in the evening after 5 weeks.[24] Subjective measures of hunger decrease after 16 weeks when adults with obesity self-selected to a 10–12 h TRE.[27] Additionally, sensations of hunger were reduced among older adults following an 8-h TRE period for 6 weeks compared to normal feeding.[28] Despite these intriguing observations, two of the studies mentioned above were done under controlled feeding conditions, thus lacking translation into a "real-world" setting,[24,26]one was a small pilot study (n=8)[27] and another was in normal-weight, midlife adults.[28] To our knowledge, no study has assessed the efficacy of TRE as a strategy for WLM (**Figure 1**). Therefore, the proposed study will target the hunger/appetite side of the equation in the energy gap to prevent weight regain after weight loss.

Beyond addressing the efficacy of TRE in the context of WLM, this study will address four other gaps in the literature. 1) Most TRE studies demonstrate heterogeneity in permitted eating windows (e.g., 10 h vs 6 h); therefore, it is unclear which intervention is feasible and acceptable. 2) Prior studies lack qualitative data on barriers and facilitators to TRE[29], including attention to factors that influence long term behavioral maintenance. 3) Prior studies often neglect baseline assessment of usual temporal eating patterns[30], only screening for breakfast consumption[31] or prior fasting. Therefore, it is unclear how eating patterns change as a result of TRE. 4) Previous studies on TRE rely on participant recall and self-report to quantify eating patterns, which are often misreported or [32,33]; therefore, the use of an objective measure of temporal eating behaviors is warranted.

Obesity and adiposity-based chronic diseases are a large health concern in the U.S., which may be explained by repeated failures to sustain long-term WLM. Given the physiological underpinnings of weight loss and the propensity for weight regain, there is an urgent need to develop and assess bio-behavioral strategies for WLM in adults with obesity. In conjunction with other determinants of WLM (e.g., self-monitoring), the long-term goal is to use TRE to develop a feasible and scalable WLM program. Understanding how to optimize and support individuals after weight loss is paramount in both preventing and treating obesity and adiposity-based chronic diseases.

2.2 Rationale

Despite short-term weight loss success most individuals fail to sustain long-term WLM. Failure to sustain WLM may be the result of biological adaptations that increase hunger following weight loss. While bio-behavioral interventions targeting WLM exist, an untested strategy for WLM is time-restricted eating (TRE). TRE does not require deliberate caloric restriction, and simply requires individuals to eat between a certain eating window (e.g., 8am to 4pm). TRE has been tested for weight loss, but the effects on WLM are unknown. Moreover, there is currently heterogeneity in the duration of the eating window and it is unclear which eating window is feasible and acceptability. Therefore, in our 12-week randomized clinical trial, we will examine the feasibility, acceptability, and adherence to the eating window in adults with recent weight loss (primary endpoints). We will conduct semi-structured qualitative interviews in a subset of participants to examine individual, family and neighborhood/community level barriers and facilitators to each TRE intervention such as motivation, cultural factors, occupation, and family structure. We will explore changes in lean mass and fat mass in each TRE intervention at 12 weeks.

2.3 Potential Risks & Benefits

Risk of fasting: Intermittent fasting (i.e., TRE) for extended periods can cause hunger, dizziness, headaches, irritability, stomach discomfort, or fainting. We will instruct participants if they report any serious periods of hunger, dizziness, headaches, irritability, stomach discomfort and risk of fainting to consume a small meal including foods that are common in your diet.

The risks associated with participating in this study on intermittent fasting for weight management will be minimized through the implementation of standard of care monitoring. This includes regularly checking in with participants to

assess their physical and mental well-being, as well as ensuring that any adverse effects or concerns are promptly addressed. Participants will be reminded to continue to see their physician of record and that study procedures are not in lieu of standard medical care.

In addition, all participants will be informed of the potential risks associated with intermittent fasting and will be given the opportunity to ask questions and express any concerns before deciding to participate in the study. The PI and study team will also closely monitor participants for any adverse effects or signs of distress and will immediately intervene as needed. Exclusion criteria (described in 5.2) will exclude at risk patients, such as those who are pregnant or trying to become pregnant, having an eating disorder or history of an eating disorder, have type 1 or other conditions that would preclude restricted eating windows, have type 2 diabetes with a HbA1c >7.0% on medications except for metformin alone, have narcolepsy, or active cancer. By implementing these measures, we aim to ensure the safety and well-being of all participants while still gathering valuable data on the effects of intermittent fasting on weight management.

There is a risk for privacy and confidentiality: to minimize these risks, a variety of measures are used which will reduce information security risk. First, all study staff will be trained in the NYULMC Research Practice Fundamentals, which include training in issues of confidentiality. All study staff will be required to sign a confidentiality agreement. Data will be maintained in separate files for identified and de-identified data in locked file cabinets in a locked office. Access to these data will be restricted to the PI (Popp), the medical co-I (Dr. Lofton), and study staff responsible for gathering data and maintaining research files. Data will be entered into a centralized database maintained on a secure server. Data in these files will be linked to participants only through their ID number. All data collected will be used expressly for the purpose of the proposed study.

- Security of data entered and stored on the myCircadianClock (mCC) app. The mCC app is maintained on the highly secure Amazon Web Services by the Salk Institute. The app is programmed by NYU study staff with the participants' study ID and password (i.e., no identifiers are used to program the mCC app). De-identified data are shared with the Salk Institute but identifies will not be provided. The participant enters eating patterns behaviors, as well as physical activity and sleep. Participants will be advised that study staff will remotely review this record. They also will be informed that there is a remote possibility that the Cloud or their mobile account could be hacked and that information about study activities (recorded diet, sleep, physical activity) could be disclosed. However, these data are not considered sensitive in nature. It is possible that a participant could lose their smart phone or leave it in a public location with the screen turned-on, enabling others to view recorded eating patterns. To address this, we will offer assistance in enabling a screen saver, to be activated when the smart phone has been idle for 5 minutes, as well as a 4-digit password that must be entered when the device is turned-on. The mCC app does not collect or transfer patient- related health information, personal identifiers, mobile phone numbers, serial numbers or any other information that can be used to identify the user. The app does use GPS sensor to tag location for logging data, which helps to monitor change in time zone, which is important in for meal timing as circadian rhythm plays a key role in human health. Participants who do not own a smart phone will be loaned a study iPhone. Loaner phones are configured with Airwatch. Airwatch is a mobile device management software program that permits remote operation of the iPhone (including disabling and wiping the device).

Risk associated physical activity/eating monitor: There is a very small risk some people who wear the physical activity/eating monitor may experience redness, itchiness and swelling. We will instruct participants if they report any issues with physical activity/eating monitors to remove them from their wrist. They will be instructed to not wear the monitors at subsequent visits.

2.3.1 Known Potential Risks

Risks of participation in this study are minimal and unlikely to occur, given the safeguards in place. Psychological risks include 1) the possibility that some participants may perceive some questionnaire or background data assessment as intrusive or causing them to feel uncomfortable, 2) breach of confidentiality and 3) possibility of redness, itching and swelling from the activity/eating monitor. Intermittent fasting (i.e., TRE) for extended periods can cause hunger, dizziness, headaches, irritability, stomach discomfort, or fainting.

2.3.2 Risk of Use of Mobile Health Technology

Commercial products or devices made by third party companies, including wearable fitness trackers, wearable sleep monitors, mobile apps for use on smartphone and tablets, websites and web apps, and types of computer software that permit screen sharing, record keystrokes, gain access to device files and/or use location tracking technology will be used to collect study data. These devices will be used in accord with the Terms of Service (TOS) and/or the End User License Agreements (EULA) provided by the product or device vendor. Use of such products and devices may result in loss of privacy and risk of breach of confidentiality. These products and devices will only be used to collect study data with IRB approval and if the subject has agreed to all applicable Terms of Service and EULAs. The participant will be advised to read the full EULA or TOS before agreeing to use the product.

2.3.3 Known Potential Benefits

There are no direct benefits to research participants outside of the potential weight management effects of the intervention.

Research on alternative strategies for WLM to prevent weight regain is limited, but important given the continuing rising obesity and adiposity-based chronic disease in the United States. This proposed study will serve as the first step to establish the evidence for TRE to be incorporated into weight management programs throughout the country. Additionally, it will provide further insight beyond the basic understanding of diet and exercise interventions by including measures of appetite.

3 Objectives and Purpose

3.1 Primary Objective

To determine the feasibility and acceptability in terms of recruitment, retention, and intervention adherence to TRE10 and TRE6 after 12 weeks using a mixed methods design.

3.2 Secondary Objectives

To determine individual, family and neighborhood/community level barriers and facilitators to each TRE intervention such as motivation, cultural factors, occupation, and family structure.

3.3 Exploratory Objectives

To explore changes in body composition (lean mass and fat mass) using BIA.

4 Study Design and Endpoints

4.1 Description of Study Design

We will conduct a 12-week, parallel arm pilot randomized clinical trial examining two TRE interventions with differing eating window durations (≤6 and ≤10 h) in adults who are overweight and obese recruited from two weight management clinics. We will assess feasibility, acceptability, and adherence of two TRE interventions. We will enroll eligible adults who have successfully completed the NYULH-WMP and NY-MOVE! Clinic programs. Prior to randomization, participants with enter an run-in phase for 4 weeks to prevent further weight loss. We will randomize participants with equal allocation to: ≤10 h (TRE10) or ≤6 h (TRE6). Measurements will occur at 0, 4 and 12 weeks. We will conduct semi-structured, qualitative interviews to capture participants' experience with TRE, understand barriers and facilitators to intervention uptake and expectations regarding long term maintenance of TRE, and identify useful strategies to enhance retention and intervention adherence. We will explore changes in lean mass and fat mass in both arms using BIA. We will recruit 50 adults with the goal of retaining 40 (n=20/arm) between the ages of 25–65 y who demonstrated a non- surgical weight loss of ≥5% of initial body weight, and a resulting BMI >20.5 kg/m^2. Participants must own a smartphone or be willing to use a study smartphone for self-monitoring and capturing the duration of their eating window.

Telephone Screening. We will screen via telephone for age, height, weight (body mass index), smartphone ownership or use, recent weight loss, medical history and medication use. Participants who meet our inclusion criteria will be schedule for a baseline measurement visit.

Baseline measurement. Potential participants will attend an in-person screening visit, signed informed consent will be obtained and we will screen for recent weight loss and BMI (measuring height and weight), and body composition (lean mass and fat mass) using BIA. Participants will download the myCircadianClock (mCC) smartphone application for dietary self-monitoring. They will be directed to track only what they eat and drink over the next 10

days. Participants will wear TWO ActiGraph GT9Xs for up to 10 days to objectively (actigraphic-based wrist motion) assess eating patterns and measure physical activity. We will review how to enter eating occasions into the mCC smartphone and answer any questions participants have regarding the app. Participants will be provided with a Bluetooth-enabled Renpho body weight scale for remote monitoring of their body weight for the run-in phase (see below). Participants will be enrolled if they: 1) log at least 2 meals into the smartphone app on ≥5 days, 3) wear the ActiGraph for ≥5 observation days and 3) their eating window is >12 h.

Run-in phase. In order to increase the probability of detecting a true treatment effect (e.g., TRE) on WLM, each enrolled participant will enter a 4 week run-in phase (separate from screening) to ensure they are weight stable prior to randomization. Participants will be given a Bluetooth-enabled Renpho body weight scale for remote recording of their body weight during the run-in. A weight stable participant is defined as one that demonstrates additional weight loss of 2.5kg following the run-in. (Weight gain during the run-in does not disqualify the individual from randomization).

TRE Interventions. Participants will be instructed to consume all food and beverages during their allotted time period (i.e., TRE6 or TRE10). Participants will self-select the timing of their first eating occasion of the day, with the provision that their first meal of the day will be consumed within 3 h of their wake- up time and finished no less than 3 h prior to bed time. During the fasting period, participants will be encouraged to drink water, and will be permitted to consume zero-calorie beverages, like diet soda, black tea, or sparkling water. Both TRE interventions will pair with self-monitoring and feedback as self-regulatory approaches to WLM. Eating occasions will be self-monitored using the mCC app, which date- and time-stamps all food entries. Participants in each arm also will be instructed to self-monitor their body weight daily using a Bluetooth-enabled Renpho scale, which permits remote collection of body weight.

Feasibility and acceptability (Aim 1.1): recruitment and retention. We will develop a recruitment funnel by documenting the total number of eligible patients completing the NYULH-WMP and NY- MOVE! programs losing ≥5% of their baseline body weight. The recruitment funnel will include the number that must be approached to enroll one participant in the pilot study who meets run-in criteria and is randomized, is retained through 12 wks, and reasons for refusal and drop-out. We will also describe enrolled participants in terms of time to weight stability following cessation of the medical weight management program.

Acceptability (Aim 1.2): Participant experience with TRE. As part of the mixed methods design, we will include an investigator-developed questionnaire called the TRE Experience Questionnaire (TRE-EQ; quantitative) and semi-structured interviews (qualitative) to quantify participants' experience with their assigned TRE intervention. The TRE-EQ will be administered online and include 11-point scaled items (0=none at all, 10=the most they can imagine) regarding difficulties encountered with hunger; eating within the assigned window; coordinating the TRE window with work, school and home demands; and accommodating social connections (e.g., behaviors and preferences of fellow diners). Using the same scale, participants will report perceived likelihood they can continue to use TRE for WLM.

At 12 weeks, 60-minute, semi-structured, qualitative interviews will be conducted in participants from each TRE arm demonstrating the lowest and highest eating window adherence (n=12/arm; n=24 total) to characterize their experience with the intervention and identify strategies to mitigate barriers and leverage facilitators that enhance retention and adherence. Two theoretical frameworks will guide the qualitative interviews: 1) social practice theory[34] and the 2) social ecological model (**Table 3**).[35] For comparability, we will build on the methods of Bjerre et al.[29] 2021 who used social practice theory during a 12-week, 10-h TRE intervention. Additionally, we will use an adapted social ecological model to identify individual, family and community/neighborhood factors that are barriers or facilitators to the TRE intervention. All of the qualitative interviews will be recorded and transcribed verbatim.

TRE eating window adherence (Aim 1.3). Adherence to the TRE window will be assessed objectively via actigraphic-based wrist motion at each measurement timepoint to characterize the objective assessment of eating patterns.[36,37] The method has been validated on the publicly available all-day dataset, which consists of recordings of wrist motion of 351 people for one full day each.[37] A day will be labeled as eating window adherent if all logged entries fall within the prescribed eating window ± 30 minutes. Participants will be directed to wear the Actigraph GT9X for 10 days on their dominant hand, remove it for bathing or swimming, recharge it as needed, and return it on day 11 to the investigators in a postage-paid return envelope.

Barriers and Facilitators (Sub Aim 1). We will use qualitative interviews to identify both barriers and facilitators to each TRE intervention, based on participants with the highest and lowest eating window adherence. In adults with obesity, social occasions or events, such as dinner or drinks after work, appear to contribute to nonadherence.[38] We will build upon these findings with the qualitative interviews guided by the social ecological model and include open-ended questions pertaining to individual motivation, family dynamic, occupation, and community/neighborhood.

4.2 Study Endpoints
Unless otherwise specified below, all measurements will occur at baseline, 4, and 12 weeks.

4.2.1 Primary Study Endpoints
The primary endpoints will be (Aim 1.1) recruitment and retention, (Aim 1.2) acceptability of participant experience using TRE Experience questionnaire (TRE-EQ) and semi-structed, qualitative interviews, and (Aim 1.3) adherence to the eating window at 12 weeks.

4.2.2 Secondary Study Endpoints
The secondary endpoints will be barriers and facilitators to each TRE intervention.

4.2.3 Exploratory Endpoints
We will explore changes in body composition (lean mass and fat mass) using BIA.

5 Study Enrollment and Withdrawal
5.1 Inclusion Criteria
In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- ≥5% non-surgical weight loss from NYULH-WMP and NY-MOVE! Endocrinology Weight Management Clinic in the last 3 months
- BMI between 20.5 - 45 m/kg^2
- between the ages 25 to 65 years old
- own a smartphone or willing to use a smartphone if provided for self-monitoring
- Eating window >12 h per day
- log at least 2 meals into the smartphone app on ≥5 days

5.2 Exclusion Criteria
An individual who meets any of the following criteria will be excluded from participation in this study:

- <25 years or >65 years of age
- Body weight in excess of 400lbs (181.4kg)
- pregnant, trying to get pregnant or breastfeeding

- previous or planned bariatric surgery
- previous or current history of eating disorder
- ongoing participation in another weight-management research study
- continued participation in a weight loss program other than the proposed study
- currently on appetite suppressants
- currently following intermittent fasting or skipping meals
- Prior weight loss from TRE or any form of fasting (e.g., alternate day fasting)
- eating window <11h 59min/day
- perform overnight shift work more than once a week
- work that includes travel across one or more time zones
- currently on anti-obesity medications (AOMs) such as, GLP-1 analogues (exenatide, tirzepatide, semaglutide, liraglutide) and pancreatic lipase inhibitors (Orlistat/Xenical and Alli)
- prescribed medications expected to result in weight loss such as Orlistat, Naltrexone, Bupropion, Lorcaserin, Phentermine, Topiramate, or Liraglutide, and who are unwilling to delay treatment with these medications for the next 3 months
- unable or unwilling to provide informed consent
- unable to participate meaningfully in the intervention (e.g., uncorrected sight and hearing impairment)
- unwilling to accept randomization assignment
- unable to log at least 2 meals into the smartphone app on ≥5 d during the screening period
- have type 1 or other conditions that would preclude restricted eating windows
- have type 2 diabetes with a HbA1c >7.0% on medications except for metformin alone
- narcolepsy
- active cancer
- organ dysfunction
- >2.5 kg additional weight loss during run-in phase (weight regain is not an exclusion criteria)

5.3 Vulnerable Subjects

No vulnerable populations are included in this study.

5.4 Strategies for Recruitment and Retention

In order to meet our recruitment goal of 20 participants per group (n=40 total) during the proposed 12-mo recruitment period, we will screen around 25–30 participants per month. Assuming 40% loss from screening to eligibility, we will enroll 12–18 participants per cohort over 4–6 cohorts. The NYULH-WMP sees over 1,900 patients each year, with approximately 40 participants enrolling in the program each month. There are currently >2,500 eligible Veterans at the Manhattan VA who are eligible. We will work with Drs. Lofton and Aleman to identify eligible graduates and develop a roster of individuals from the of NYULH- WMP and NY-MOVE! Clinic.

5.4.1 Recruitment

The privacy of potential participants will be maintained during all recruitment efforts, including direct subject encounters. Personal identifying information, such as names and contact information, will be collected only with the explicit consent of the potential participant and will be kept confidential. During any direct subject encounters, such as in-person meetings or phone calls, the researcher(s) will take steps to ensure that the participant's privacy is maintained. This may include conducting the encounter in a private location or using a secure phone line. Any personal information collected during these encounters will be kept confidential and stored securely. The confidentiality of all identifiable data collected during recruitment for this study will be strictly maintained. In the event that a potential participant does not meet the inclusion criteria for the study (i.e. a "screen failure"), any identifiable data collected during the recruitment process will be destroyed immediately after the recruitment period has ended. All personal identifying information will be removed from the data and any remaining de-identified data will be securely destroyed. The confidentiality and privacy of potential participants who do not meet the inclusion criteria for the study will be respected and protected at all times.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact Dr. Popp or have subjects contact research-contact-optout@nyumc.org or 1-855-777-7858.

For NYULH-WMP and NY-MOVE! clinic, the study team will develop a communication plan and materials that

introduce the study to patients and their providers. To replicate our recruitment successes in prior studies, we will adapt the following materials for this study:

- A one-page description of the project: Introducing the overarching goals and rationale and what is expected of participants.
- Frequently asked questions (FAQ) document: FAQs will be available as one-page document.
- Waiting Room Advertisements: Flyers, poster boards, and electronic posters for display in clinic waiting rooms and exam rooms with content similar to the one-page description (above) that include study contact information.
- Poster boards and flyers: For community outreach, health fairs, community events.
- Study recruitment video: A brief study recruitment video will be featured that also can be sent via email as a link to providers and patients. Dr. Sevick's group has extensive experience with video creation for use in clinical trials.
- Prepared talks and slide decks: For faculty meetings to introduce the study to providers at NYULH and the VA.
- Posts on Other websites: We will post information on Clinicaltrials.gov, the NYU Langone Clinical Trials Webpage, and the NYU Langone Comprehensive Program on Obesity Website.
- Use of tailored recruitment materials: We anticipate that it may be more challenging to recruit underrepresented groups (e.g., African American, male patients). The PI and his mentors have a strong track record of recruiting diverse men and women into our studies, facilitated by the use of tailored recruitment materials featuring diverse patient populations and by multi-cultural staff.
- Use of people-first language and positive obesity-related images: People with obesity are subject to stigma and bias. We will use people-first language as recommended by the Obesity Action Coalition to ensure that all participants feel valued and respected.

5.4.2 Use of DataCore/Epic Information for Recruitment Purposes

We will use EPIC to identify potentially eligible patients seen in NYUMLC Faculty Group Practices and NYUMLC affiliates. A listed of DRG codes indicating presence of overweight, or obesity will be proved to DataCore who will generate a roster of potential participants' names, emails, phone numbers, and addresses. The PIs and research data associates will all have access to the EPIC search results. The data points and PHI that will be used for the search will be: overweight or obesity diagnoses codes, DOB. Frequency of EPIC queries will depend on recruitment success. We anticipate running EPIC queries every month until target participant numbers are met. We will maintain the roster for the duration of the study and the study staff will monitor EPIC three times per week.

We will use one of two methods described below to recruit eligible participants. The method choice for enrolling participants will be contingent on the treating physician's (TP) stated capacity for the quantity of their patients that they can review and recommend for study participation, and whether participants self-refer to the study:

Method 1: Clinical-Initiated contact with TP review prior to pre-screening

We will develop a roster of potentially eligible patients for each treating physician in the practice. Physicians will be asked to review the roster and indicate, for each patient, whether an intervention targeting weight loss is appropriate. Lists of patients deemed appropriate (i.e., "yes") by the physician will be generated. Following written permission from NYULMC treating physicians to recruit their patients to the study, patients will be approached and screened using the following process: (a) A letter signed by the treating physician and Dr. Sevick will be sent to the treating physician's patients notifying them of the study, and informing that an NYULMC clinical staff person will contact them to explore their willingness to consider participation, or that their patients can call directly to the study staff to ask about the study. (b) An NYULMC clinical staff person will contact these patients to briefly describe the study and request their permission (yes/no) for study staff to contact them directly by telephone. (c) We will call patients who agree to be contacted, describe the study and if the patient expresses an interest, conduct preliminary screening by telephone. Verbal agreement obtained by study staff prior to eligibility screening. (d) Written informed consent will be obtained with subsequent face-to-face measurement visit to the 180 Madison for eligible participants.

Method 2: Clinic-initiated contact with TP review post pre-screening

We will develop a roster of potentially eligible patients for each treating physician in the practice. Following written permission from NYULMC treating physicians to recruit their patients to the study, patients will be approached and screened using the following process: (a) A letter signed by the treating physician and Dr. Sevick will be sent to the

treating physician's patients notifying them of the study, and informing that an NYULMC clinical staff person will contact them to explore their willingness to consider participation, or that their patients can call directly to the study staff to ask about the study. (b) An NYULMC clinical staff person will contact these patients to briefly describe the study and request their permission (yes/no) for study staff to contact them directly by telephone. (c) Study staff will call patients who agree to be contacted, describe the study and, if the patient expresses an interest, conduct preliminary screening by telephone. Verbal agreement is obtained by the study staff prior for eligibility screening. (d) These participants will be told that the study staff needs to verify suitability for this study with their treating physician and will be getting another call with the TP's decision. (e) Physicians will be asked to review the roster of patients eligible after preliminary screening by telephone to indicate, for each patient, whether an intervention targeting weight loss is appropriate. (f) Those patients deemed appropriate (i.e., "yes") would be scheduled for subsequent face-to-face visit to the 180 Madison to obtain written informed consent, and subsequently, measurement for eligible participants.

Method 3: Research staff-initiated contact with TP review prior and post pre-screening
We will develop a roster of potentially eligible patients for each TP in the practice. Physicians will be asked to review the roster either prior (method 1) or post (method 2) pre-screening. Following written permission from NYULMC FGP physicians to recruit their patients to the study, patients will be approached and screened suing the following process: (a) A letter signed by the treating physician and Dr. Sevick will be sent to the treating physician's patients notifying them of the study, and informing that an NYULMC research staff person will contact them to describe the study, or that their patients can call directly to the study staff to ask about the study. These patients will also be informed of an alternative for opting out of research studies. (b) Research study staff (instead of clinic staff) will call patients who agree to be contacted, describe the study and, if the patient expresses an interest, conduct preliminary screening by telephone. Verbal agreement is obtained by study staff prior to eligibility screening.

Thereafter, the steps for Method 3 follow either Method 1 or 2 depending whether treating physicians decide to screen their patient list for eligibility prior or after research staff calls their patients.

Method 4: Participant self-referral through EPIC electronic health record MyChart alerts
We will provide the NYU Langone Health Epic Research Integration team with lists of potentially eligible patients provided to us by NYU Langone Health DataCore services. The Epic team will send these patients an alert notification to inform patients to check MyChart electronic record for a new message. We will provide an NYU Langone Health Epic Research Integration team with an IRB-approved patient-facing message to be posted in the Epic electronic health record patient portal (MyChart) with a brief study description with information for patients to contact study staff for any questions or to express their interest to participate. At this point, study recruitment proceeds as per protocol: (a) study staff describe the study and, if the patient expresses an interest, conduct preliminary screening by telephone. Verbal agreement is obtained by study staff prior to eligibility screening. (b) Written informed consent will be obtained with subsequent face-to-face measurement visit to the CTSI for eligible participants.

If a participant requests information regarding opting out of further recruitment for all research, participants will be directed to contact collin.popp@nyulangone.org.

Method 5: Participant self-referral through send [SAFE] email messages
Given that many potential participants on the DataCore list are not MyChart active and/or have not opened their MyChart messages, potential participants will be sent the same IRB-approved recruitment message to their personal emails via send [SAFE], a NYU Health secure messaging server. Emails will be obtained from the DataCore list provided. No recruitment materials be used until they have been submitted and approved by the IRB.

5.1 Informed Consent Process

5.1.1 Consent/Assent and Other Informational Documents Provided to Participants
Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention. The following consent materials are submitted with this protocol: Telephone Consent and Informed Consent.

5.1.2 Consent Procedures and Documentation

A brief description of the study will be provided via telephone at the time of screening for the study. We will verify eligibility. Signed informed consent will be obtained from remaining eligible participants.

Once approved by the IRB, participant will be consented via REDCap e-consent framework. Participants will be emailed a REDCap link containing both the informed consent and audio-visual consent and a Webex meeting will be scheduled to review these documents. At this time, we will review the consents with the participants and participant will electronically sign and date consents, to be followed by electronic signature and date by the consenter. All questions will be answered. A copy of both the informed consent form and audio-visual consent form electronically signed by both participant and consenter will be given to the participant and they will be encouraged to contact the PI with any and all questions that occur at any time during the conduct of the study. We will follow SOP: Informed Consent Process for Research (HRP-090). At this time, we will enroll only English-speaking participants, because the proposed software is currently only available in English. The REDCap eConsent link will be submitted to the IRB for review in Research Navigator via Modification before use in the study. Language consistency with the IRB-approved consent will be reviewed and approved by the IRB before use.

Regardless of recruitment approach used, signed informed consent will be obtained at the screening visit, prior to obtaining measurements. Participants will be provided ample time to review the consent form. An investigator or study staff person will view each section with the participant, ask the participant if they understand each section, and clarify any questions they may have. The participant and the person obtaining consent will sign and date the consent form. A copy of the consent will be placed in the participant's medical record. Informed consent will be considered an ongoing process throughout the study, and participants' questions regarding their rights and responsibilities will be addressed whenever they occur.

5.2 Total Number of Participants and Sites

Recruitment will end when approximately 50 participants are enrolled. We will screen around 25–30 participants per month. Assuming 40% loss from screening to eligibility, we will enroll 12–18 participants per cohort over 4–6 cohorts. It is expected that approximately 50 participants will be enrolled in order to produce 40 evaluable participants.

5.3 Participant Withdrawal or Termination

5.3.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Failure to respectfully participate in the intervention requirements
- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.3.2 Handling of Participant Withdrawals or Termination

In the event that involuntary withdrawal is required, participants will be referred back to their treating physician of record for evaluation and management. Data collection will cease at the time of withdrawal. Data up until the point of withdrawal will be used in the analysis.

AEs, *serious adverse events (SAEs), and unanticipated problems (UAPs)* will be recorded, and the participant's treating physician will be notified. *We do not anticipate the safety of participants to be compromised upon voluntary termination. Replacements are not allowed In the event of participant withdraw from the intervention.*

5.4 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Popp (PI) and the NIH. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Procedures and Schedule

6.1 Study Procedures/Evaluations

6.1.1 Study Specific Procedures

Medical history*:* Demographics, emergency contact information, background information (i.e., gender, DOB), income and General Health information will be collected by questionnaire during screening visit.

Medication history: medication history will be completed during screening or prior to screening visit. A complete medication history (current and previous), that includes over-the-counter and prescription medications will be collected to assess for eligibility.

Physical examination: Height (centimeters) and weight (kilograms) will be collected to assess BMI at screening. Weight will be assessed again at 4, and 12-weeks. Body composition will be collected to assess lean mass (kilograms) and fat mass (kilograms) at screening using BIA (InBody 270).

mCC app: the app will be used to self-monitor eating patterns and downloaded to the participants' smartphones for the duration of the intervention. Participants will be directed to enter data about foods and beverages. The app sends occasional reminders to complete study activities.

Adherence: Study staff will routinely monitor participants' mCC dashboards and will be available for answering questions about meal entry to assure adherence to measurement protocol.

Physical Activity and eating patterns: During screening, 4 and 12-weeks, participants will wear an ActiGraph GT9X to measure physical activity and objectively assess eating window. The activity monitor measures physical activity, sleep and wrist-motion. Study staff will contact participants to assure adherence to protocol.

6.1.2 Standard of Care Study Procedures

During this study, we will monitor participants' weights as part of endocrinology standard of care. Participants will be reminded to continue to see their physician of record and that study procedures are not in lieu of standard medical care.

6.2 Study Schedule

6.2.1 Screening

Telephone Screening (Day -38 to -52)

- A brief description of the study (TRE groups, length, number of visits) will be provided and asking if they are interested
- Screen for: age, height, weight, recent weigh loss, medical conditions, owning or using a smartphone, and engage in study activates
    - Notify them the call and the following questions are considered a screening process. If they are eligible and agree to participate in this study, we will have them sign an informed consent at the measurement visit.
- Screen participants over telephone to determine eligibility.
- If participants fail screening, they will be offered information about other studies in the department that may pertain to them or alternative programs they can join
- If participants are eligible, we will schedule a baseline visit.

Baseline Visit (Day -38 to -28) at 180 Madison Ave, Department of Population Health

- Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Administer questionnaires via RedCap: Morningness Eveningness Questionnaire, Apnea/Epworth Sleepiness Scale, Insomnia Severity Index, Weight Efficacy Lifestyle Questionnaire, Self-efficacy for exercise scale
- Measure height (cm), weight (kg)
    - If participants have a BMI below 20 or above 45 kg/m^2, participants will not be consented and will be dismissed with payment for visit
    - Participants with body weight in excess of 400lbs will also be dismissed
- Measure body composition (lean mass and fat mass) using bioelectrical impedance analysis (BIA) test
    - Participants will be asked if they have an implantable device- participants with implantable devices will skip the BIA measurement
- A copy of the informed consent will be given to eligible participants
- Download the MyCircadian Clock (mCC) smartphone application and instruct them on how to enter foods and beverages into the app.
- Fit ActiGraph activity watch to measure physical activity, sleep and eating patterns. Participants will wear for up to 10 days
- Provide postage-paid return box for return of activity monitor to investigators.
- Provide participants with Renpho scale and instruct them on the use for the run-in phase.

Run-In Period (-28 days to 0), no visit

- Participants will weigh themselves daily for 4 weeks (28 days) and will enter foods into the mCC app.
    - Participants who log at least 2 meals into the smartphone app on ≥5 days over 10 days during the run-in period to be eligible.
- Participants will return both ActiGraphs via pre-paid postage.
- Participants will be enrolled if they wear the ActiGraph for ≥5 observation days, their eating window is >12 h, and maintain WLM of ± 2.5 kg during run-in phase
- We will call participants if they are eligible.

6.2.2 Enrollment/Baseline

Enrollment/Intervention Period begins (Visit 1, Day 0)

- One-on-one phone call session with study team to review intervention goals based on randomization assignment
    - TRE6: restrict eating window to 6 hours per day
    - TRE10: restrict eating window to 10 hours per day

6.2.3 Intermediate Visits

4 week (Visit 2, Day 31 +/- 14 days) at 180 Madison Ave, Department of Population Health

- For all participants:
    - Measure body weight
    - Perform a bioelectrical impedance analysis (BIA) test; participants will be asked if they have an implantable device- participants with implantable devices will skip the BIA measurement
    - Administer TRE-EQ questionnaire
- Record adverse events as reported by participant or observed by investigator.
- Provide ActiGraph GT9X activity monitor to assess physical activity, sleep and eating patterns.
- Provide postage-paid return box for return of activity monitor to investigators

6.2.4 Final Study Visit

12-week visit (Visit 3, Day 91 +/- 14 days) at 180 Madison Ave, Department of Population Health

- The 12-week visit will be identical to the 4-week visit.
- For all participants:
  - Measure body weight
  - Perform a bioelectrical impedance analysis (BIA) test; participants will be asked if they have an implantable device- participants with implantable devices will skip the BIA measurement
  - Administer TRE-EQ questionnaire
- Record adverse events as reported by participant or observed by investigator.
- Provide ActiGraph GT9X activity monitor to assess physical activity and eating patterns.
- Provide postage-paid return box for return of activity monitor to investigators
- At the conclusion of the study or at the time of withdrawal, participants will be sent a one-page handout with their personal results, and a copy of the study primary outcomes paper.

Subgroup semi-structured interviews via WebEx (Visit 4 [not in person], Day 91 +/- 14 days)

- In participants (n=24, n=12/arm) with low and high adherence to their randomized eating window, we will conduct semi-structured qualitative interviews lasting 60-minutes
- We will conduct these interviews via WebEx and the interviews will be audio and video recorded.

6.2.5 Withdrawal/Early Termination Visit

See Handling of Participant Withdrawals or Termination,

6.2.6 Unscheduled Visit

Unscheduled visits by participants will be instructed to return during scheduled visits for data collection. These visits will be documented.

6.3 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications and dosage amounts taken during study participation will be recorded on CRF. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications. Medication information will be collected at screening and measurement visits. Anti-obesity medications (AOMs) that are taken by participants in the study may directly or indirectly impact the study. Because all patients will continue to receive standard care, all that we can do is to monitor the medications and note any changes.

6.4 Justification for Sensitive Procedures

6.4.1 Precautionary Medications, Treatments, and Procedures

Not applicable.

6.5 Prohibited Medications, Treatments, and Procedures

See exclusion criteria for list of prohibited medications.

6.6 Prophylactic Medications, Treatments, and Procedures

No medications, treatments or procedures will be provided as prophylaxis.

6.7 Participant Access to Study Agent at Study Closure

Participants will be provided with their physical activity logs and body composition results from the BIA at the conclusion of the study. They will be sent a copy of the pilot study paper upon its publication.

7 Assessment of Safety

7.1 Specification of Safety Parameters

7.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

7.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- <u>Suggests that the research places subjects or others at greater risk of harm</u> (including physical, psychological, economic, or social harm).

7.2 Classification of an Adverse Event

7.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

7.2.2 Relationship to Study Intervention

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

7.2.3 Expectedness

The PI (Sevick) will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

7.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UAPs will be recorded in the data collection system throughout the study.

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

The PI (Sevick) will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any

death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

7.4 Reporting Procedures – Notifying the IRB

7.4.1 Adverse Event Reporting

The PI (Sevick) will report an AE via Research Navigator to the IRB within 5 working days of learning about the event. The report will include a narrative summary of all events surrounding the AE.

7.4.2 Serious Adverse Event Reporting

The PIs (Sevick/Popp) will oversee the study to ensure data being collected is accurate and relevant to the study question. The PI and Project Manager will monitor any safety issues that arise. Information on any office visits occurring between study visits, and changes made to medications will be carefully tracked and recorded in the appropriate sections of the Case Report Forms at the next scheduled study visit. Follow-up forms will be completed in accordance with standard AE/SAE reporting guidelines. All AE/SAEs will be evaluated for seriousness, severity, and causality by the PI, and bariatric surgeons. The IRB will be notified of reportable events on an annual basis or more often as required.

Should a patient experience a serious, unexpected adverse event (SAE), it will be reported to the IRB within 24 hours of learning of the event, using an SAE report form. As this is an exploratory study, there are no foreseeable stopping rules for the entire study at this point.

7.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UAPs require the creation and completion of an UP-report form. It is the site investigator's responsibility to report UAPs to their IRB and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UAPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor immediately after the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 5 working days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 10 workings days of the IR's receipt of the report of the problem from the investigator.

7.4.4 Reporting of Pregnancy

If at any point during the duration of the study (i.e., screening, intervention) a participant becomes pregnant, they will be excluded from further continuation of the study.

7.5 Reporting Procedures – Notifying the Study Sponsor

The study clinician (Lofton) will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

7.6 Study Halting Rules
There are no predefined halting rules in place. We do not foresee temporary suspension of enrollment and/or study intervention due to the intent to treat nature of the study intervention.

7.7 Safety Oversight
It is the responsibility of the PIs (Sevick) to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of AE as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. The PI (Sevick) and co-Is (Popp and Lofton) are responsible for data safety monitoring reviews. This includes conducting systematic and periodic reviews of aggregate data and adverse events. These specific data and events include: body weight and AE. These data and events will be reviewed once per month and a summary report will be disseminated to the research team via hardcopy or email. We will include Dr. Lofton in data safety monitoring, and share with her any SAE or AE.

No predefined stopping rules will be used given this study an exploratory, feasibility study.

A summary of the outcomes of these safety reviews along with accumulated adverse events and deviations will be submitted to the IRB as part of an annual progress report at the time of the Continuing Review submission.

8 Clinical Monitoring
Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the PIs (Sevick)
- On-site monitoring (e.g., on-site, centralized) will begin when the first subject is enrolled and every week thereafter as needed.
- Independent audits will be conducted by study sponsor to ensure monitoring practices are performed correctly at the site

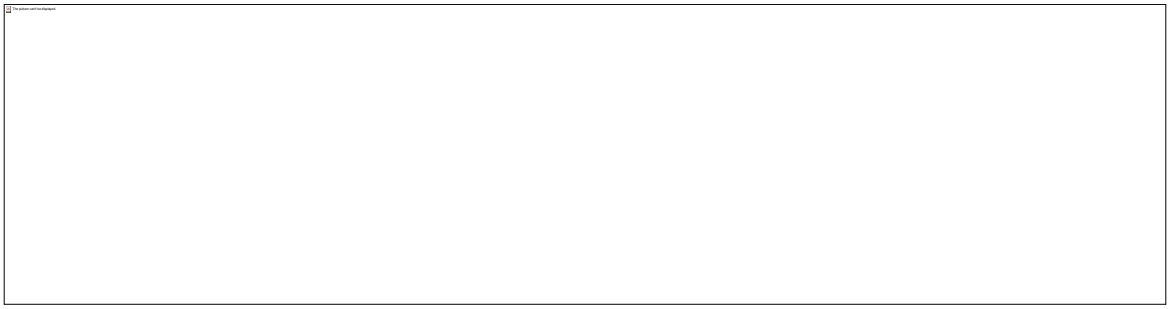
9 Statistical Considerations
9.1 Statistical and Analytical Plans (SAP)
There is no formal SAP.

9.2 Statistical Hypotheses
The study is a pilot feasibility and acceptability study; therefore, there is no formal hypothesis being tested.

9.3 Analysis Datasets
An "intent-to-treat" (ITT) approach will be used to address the specific aims. All participants will be included in the data analysis in the treatment arm to which they were randomized, regardless of compliance, treatment received, or deviation from protocol. Data from participants who withdraw will be used to the extent permitted by human subjects and privacy considerations

9.4 Methods
9.4.1 General Approach
A sequential mixed model design (Figure 1) will incorporate quantitative (eating window adherence, TRE questionnaire) and qualitative (interviews) data to ultimately select the TRE intervention most feasible and acceptable (Research Aim 1). Additionally, we will identify barriers and facilitators to each TRE intervention (Sub-

aim 1).



9.4.2 Analysis of the Primary Efficacy Endpoint(s)

Feasibility. To assess the feasibility of the TRE intervention, we will determine the number and percent of participants dropping-out of each arm, as well as reasons for drop-out. **(2) Acceptability.** We will access acceptability of the TRE interventions using the *TRE Experience Questionnaire (TRE-EQ),* which is described in the *Protection of Human Subjects* section. We will complement the quantitative data on participant acceptability with qualitative interviews conducted at 12-weeks. We will identify and categorize themes related to acceptability of each TRE intervention. **(3) Adherence:** We will access eating window adherence to the TRE interventions using the ActiGraph GT9X wearable device. We will analyze the data using the algorithm developed previously described. Briefly, the classifier detects a pattern of wrist-roll motion associated with a bite through the detection of four events. First, the wrist roll velocity must surpass a positive threshold. Second, a minimum amount of time must pass. Third, the velocity must surpass a negative threshold. Finally, a minimum time must pass between the negative wrist roll for one bite and the positive wrist roll for the beginning of the next bite. The minimum times help reduce false positives during other motions. These data are used to detect eating events from the time-stamped ActiGraph data. Data from the ActiGraph GT9X will be downloaded, de-identified and upload to an NYULH HIPPA-compliant data cloud sharing service (i.e., OneDrive). We will determine the timing of first and last eating occasions, the mean eating window during the observation period, and change from baseline.

Quantitative data analysis: A descriptive analysis of all data collected at each time point will be performed on measures of feasibility, acceptability and eating window adherence using appropriate graphical and numerical exploratory data techniques. We will assess data quality and completeness, and identify features of the data that may necessitate special methods (e.g., excess zeros, missing data, and departures from distributional assumptions). Continuous variables will be assessed for normality, and transformations will be used for non- normally distributed data. Logistic regression will be used to explore predictors of TRE intervention eating window adherence from (1) group assignment, (2) prior weight losses achieved through NYULH-WMP or Weight Management Clinic at Manhattan VA, and (3) sociodemographic characteristics (e.g., age, race). Linear regression models predicting reduction in the eating window and adherence from the patient experience will be run separately for data obtained from the acceptability and feasibility of intervention scores at 2 weeks and 12 weeks. Statistical analyses will be performed using SPSS Version 25.0.0.2 software (IBM Corp, Armonk, NY, USA).

9.4.3 Analysis of the Secondary Endpoint(s)

Qualitative Data Analysis: Transcribed interviews will be entered into ATLAS.ti, a qualitative data analysis software for data organization and analysis. We will use *thematic analysis* to analyze the qualitative data. Transcripts will be read and re-read to promote content familiarity. Data will be analyzed by line-by-line coding to allow themes to emerge. Once identified, these themes will be labelled and grouped to create higher-order themes. The coding and list of themes will be developed by Dr. Popp and the RDA, with Dr. Islam reviewing and accepting the coded transcripts and list of themes. Discrepancies in coding will be discussed and resolved, then the process is repeated with a new set of transcripts until an acceptable level of inter-coder reliability between them has been achieved, estimated using an appropriate chance-corrected statistic (e.g., kappa for nominal data and T-index for ordinal data).

9.4.4 Safety Analyses

There are no predefined halting rules in place. We do not foresee temporary suspension of enrollment and/or study

intervention due to the intent to treat nature of the study intervention.

9.4.5 Adherence and Retention Analyses

TRE Adherence. Using date from the ActiGraph on eating patterns, a day will be labeled "adherent" if all eating occasions (food or beverage with caloric value) are measured inside (± 30 minutes) their prescribed eating window. We will determine adherence by dividing the total number of adherent days by the total number of days with a logged eating occasion, regardless of whether the logged event was within the eating window. We will determine weekly percent adherence by dividing the total number of adherent days by seven.

9.4.6 Baseline Descriptive Statistics

Baseline characteristics between groups will be examined using descriptive statistics for sociodemographic, medical, and anthropometrics factors including age, height/weight/BMI, BIA output.

9.4.7 Planned Interim Analysis

No interim analysis is planned as the trial treatment is nontoxic and based on our previous experience, we don't expect the high variability of the efficacy of treatment.

9.4.8 Additional Sub-Group Analyses

In logistic regression models, we will explore predictors of the TRE intervention adherence and feasibility which will include sociodemographic characteristics such as race, sex, age.

9.4.9 Tabulation of Individual Response Data

Individual participant data will be listed by time point.

9.4.10 Exploratory Analyses

We will describe changes in relative (%) and absolute (kg) lean mass and fat mass at baseline, 4 and 12 weeks.

9.5 Sample Size

We are interested in estimates of feasibility, acceptability and adherence of each TRE intervention in terms of recruitment, retention, and adherence. We expect to enroll 12 - 18 participants per cohort and expect to begin a new cohort every month. In order to be conservative, we project a dropout rate similar to what was observed by Yancy et al.[39] (15%) and will also take into account additional dropouts and loss to follow up due to the 4-week run in phase (5%). Therefore, we will recruit and enroll 50 participants and retain 20 participants/arm, with a total of 40 participants completing the study.

At 12-weeks, we will perform qualitative interviews in high and low eating window adherent participants (n=24 total; n=12/arm). The rationale for this sample size is as follows. Thematic analysis will be used to analyze the qualitative data in the K99 phase. Based on suggested power calculations using thematic analyses[40], we seek an adjusted population theme prevalence of 15%, 4 desired number of theme instances and 80% power to find the common theme. Additionally, under the assumption of *saturation* in qualitative design, Guest et al.[41] conducted 60 interviews and found that saturation of themes was reached by the 12th interview. Therefore, given the proposed research is exploratory, we believe 24 participants (n=12/arm) are adequate for the qualitative interviews.

9.6 Measures to Minimize Bias

9.6.1 Enrollment/Randomization/Masking Procedures

Participants will be randomized using computer-generated permuted blocks and equal allocation to *TRE6* or *TRE10*. Rolling enrollment will occur with the goal of 4 - 6 cohorts of 12 -18 participants until a sample size of 50 participants have been randomized. A new cohort will be randomized every 4 weeks during a 15-month recruitment period. Those running the statistical analysis (Huilin Li) will be blinded to participant allocation. All study staff (except Huilin Li) will be unblinded to randomization. Participants will also be blinded to group assignments until the start of their respective interventions.

10 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12 Ethics/Protection of Human Subjects

12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46.

12.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3 Participant and Data Confidentiality

Information to be obtained from participants includes height, weight, physical activity, sleep and eating patterns from activity monitor, investigator-administered questionnaires (sociodemographics, comorbid conditions, and TRE-EQ).

None of the data to be collected is considered sensitive in nature. Other data (e.g., height, weight, and surveys) will be linked to the participant through an ID number. We will maintain separate files for identified and de- identified

data in locked file cabinets in a locked office. Access to these data will be restricted to the PI (Popp), the co-Is (Dr. Islam), medical co-I (Dr. Lofton), study staff responsible for gathering data and maintaining research files. Data will be entered into REDCap. Data in these files will be linked to participants only through their ID number. All data collected will be used expressly for the purpose of the proposed study. De- identified data related to actigraphy for the eating pattern subgroup will be shared through Clemson University's HIPAA-compliant Box cloud drive. This will be accessed by Dr. Adam Hoover, a professor in Clemson University's Electrical and Computer Engineering Department, and his study team. The purpose of this to measure eating patterns with the activity monitors to for objective assessment of adherence.

All WebEx videoconferencing recordings will be treated as confidential and will only be accessed by the PI (Popp), co-I, and study staff for the purpose of analyzing the data. As previously mentioned, these recordings will be securely stored and password protected. Any personal identifying information, such as names and personal contact information, will be removed from the recordings before they are shared or analyzed. Participants will be informed of the confidential nature of the videoconferencing recordings and will be asked to agree to the terms of confidentiality before participating in the study. By agreeing to participate in the study, participants acknowledge that their data may be used for research purposes, but that their identity and personal information will be kept confidential and secure. Subjects will be instructed not to verablize their names or any other identifiable information.

Measures to be used to protect subjects' privacy interests are described above. Data collection will occur in a private setting where there is no opportunity for the participants' responses to be overheard. Participants will be told that they can refuse to respond to any questions that make them uncomfortable, and that they can withdraw from the study at any time.

A variety of measures will be used to prevent breaches of confidentiality. First, all study staff will be trained in the NYULMC Research Practice Fundamentals, which include training in issues of confidentiality. As private information is collected as part of this study, there is a risk to participants' privacy and confidentiality. The research staff will take every precaution to protect participants' identity and the confidentiality of the information collected. the mCC app will be programmed by study staff with participants' age, gender, height, weight, dietary recommendations, a study ID number and a password.
Participants will be asked to enter their health behaviors (ie., food, body weight) into mCC app. The mCC app was created by and is managed by Dr. Satchidananda Panda's lab at the Salk Institute for Biological Studies. It is HIPAA compliant and double-encrypted. Participants will be consented to using the mCC app. The mCC app uses encrypted methods to transmit data between the app and the database. The use of the app for research studies has been reviewed and approved by the Institutional Review Board of the Salk Institute. The following personal health information will be collected by the app: country, language, photos or names of food/beverages you take, activity/exercise, sleep, and health entries, timestamp of entries, and geographic location data from entries. Several steps will be taken to protect participant privacy and the privacy their app data. Whenever app data is transferred to a research study computer, it will be encrypted so that others cannot interpret the data or associate it back to you. Encrypted app data (stripped of personal identifiers and associated only with a random code) will be sent to secure data servers used for the myCircadianClock research study. Participant encrypted data will be sent to a secure database where it will be stored with a unique identifier. The identifier does not contain any personal information. The participants will also receive encrypted data back from the server for visualization on their phone. App-generated data is associated only with a random participant code, and this code is used in all future analyses separating it from any personally identifiable information. Data will be de-identified and used on secure computers, but complete privacy is not ensured. These steps ensure that researchers analyzing the coded study data will not be able to connect it to any individual user.

13 Data Handling and Record Keeping

13.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PIs (Sevick/Popp). The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original

entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into RedCap, a data capture system provided by the NYU HHC CTSI. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Some of the participant (e.g., height, weight, and surveys) will be linked to the participant through an ID number. We will maintain separate files for identified and de-identified data in locked file cabinets in a locked office. Access to these data will be restricted to the PI (Popp) and his staff - all of whom will be trained in ethical research practices. Data will be entered into REDCap. Data in these files will be linked to participants only through their ID number. All data collected will be used expressly for the purpose of the proposed study.

13.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 30 working days of identification of the protocol deviation, or within 30 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents, reported to NHLBI Program Official and NYU.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

13.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the

cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

14 Study Finances

14.1 Funding Source

This study is financed through a grant from the NIH-NHBLI.

14.2 Costs to the Participant

Neither the patient nor the patient's health insurance will be billed for any study activities, tests, or procedures. The cost of all procedures and tests will be covered by funds received from the NIH.

14.3 Participant Reimbursements or Payments

Each participant will be paid $25.00 for baseline, 4 and 12 week visits (3 visits; $75.00 total) as compensation for their time and transportation costs.

15 Study Administration

15.1 Study Leadership

Not applicable.

16 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NHLBI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

17 References

1. Nicklas JM, Huskey KW, Davis RB, Wee CC. Successful Weight Loss Among Obese U.S. Adults. *Am J Prev Med*. 2012;42(5):481-485. doi:10.1016/j.amepre.2012.01.005
2. Magkos F, Fraterrigo G, Yoshino J, et al. Effects of Moderate and Subsequent Progressive Weight Loss on Metabolic Function and Adipose Tissue Biology in Humans with Obesity. *Cell Metab*. 2016;23(4):591-601. doi:10.1016/j.cmet.2016.02.005
3. Christiansen T, Bruun JM, Madsen EL, Richelsen B. Weight Loss Maintenance in Severely Obese Adults after an Intensive Lifestyle Intervention: 2- to 4-Year Follow-Up*. *Obesity*. 2007;15(2):413-420. doi:10.1038/oby.2007.530
4. Anderson JW, Vichitbandra S, Qian W, Kryscio RJ. Long-term weight maintenance after an intensive weight-loss program. *J Am Coll Nutr*. 1999;18(6):620-627. Accessed August 18, 2019. http://www.ncbi.nlm.nih.gov/pubmed/10613414
5. Weiss EC, Galuska DA, Kettel Khan L, Gillespie C, Serdula MK. Weight regain in U.S. adults who experienced substantial weight loss, 1999-2002. *Am J Prev Med*. 2007;33(1):34-40. doi:10.1016/j.amepre.2007.02.040
6. Anderson JW, Konz EC, Frederich RC, Wood CL. Long-term weight-loss maintenance: a meta-analysis of US studies. *Am J Clin Nutr*. 2001;74(5):579-584. Accessed March 27, 2018. http://www.ncbi.nlm.nih.gov/pubmed/11684524
7. Melby CL, Paris HL, Foright RM, Peth J. Attenuating the Biologic Drive for Weight Regain Following Weight Loss: Must What Goes Down Always Go Back Up? *Nutrients*. 2017;9(5):468. doi:10.3390/nu9050468
8. MacLean PS, Bergouignan A, Cornier MA, Jackman MR. Biology's response to dieting: the impetus for weight regain. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2011;301(3):R581-R600. doi:10.1152/ajpregu.00755.2010
9. Ravussin E, Bogardus C. Relationship of genetics, age, and physical fitness to daily energy expenditure and fuel utilization. *Am J Clin Nutr*. 1989;49(5):968-975. doi:10.1093/ajcn/49.5.968
10. Korth O, Bosy-Westphal A, Zschoche P, Glüer CC, Heller M, Müller MJ. Influence of methods used in body composition analysis on the prediction of resting energy expenditure. *Eur J Clin Nutr*. 2007;61(5):582-589. doi:10.1038/sj.ejcn.1602556
11. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. *New England Journal of Medicine*. 2011;365(17):1597-1604. doi:10.1056/NEJMoa1105816
12. Cummings DE, Weigle DS, Frayo RS, et al. Plasma Ghrelin Levels after Diet-Induced Weight Loss or Gastric Bypass Surgery. *New England Journal of Medicine*. 2002;346(21):1623-1630. doi:10.1056/NEJMoa012908
13. de Luis DA, Gonzalez Sagrado M, Conde R, Aller R, Izaola O. Decreased Basal Levels of Glucagon-Like Peptide-1 after Weight Loss in Obese Subjects. *Ann Nutr Metab*. 2007;51(2):134-138. doi:10.1159/000103273
14. Adam TCM, Jocken J, Westerterp-Plantenga MS. Decreased Glucagon-like Peptide 1 Release after Weight Loss in Overweight/Obese Subjects. *Obes Res*. 2005;13(4):710-716. doi:10.1038/oby.2005.80
15. Essah PA, Levy JR, Sistrun SN, Kelly SM, Nestler JE. Effect of weight loss by a low-fat diet and a low-carbohydrate diet on peptide YY levels. *Int J Obes*. 2010;34(8):1239-1242. doi:10.1038/ijo.2010.48
16. Nymo S, Coutinho S, Eknes P, et al. Investigation of the long-term sustainability of changes in appetite after weight loss. *Int J Obes*. 2018;42(8):1489-1499. doi:10.1038/s41366-018-0119-9
17. Strohacker K, McCaffery JM, Maclean PS, Wing RR. Adaptations of leptin, ghrelin or insulin during weight loss as predictors of weight regain: A review of current literature. *Int J Obes*. 2014;38(3):388-396. doi:10.1038/ijo.2013.118
18. Sherman H, Genzer Y, Cohen R, Chapnik N, Madar Z, Froy O. Timed high-fat diet resets circadian metabolism and prevents obesity. *The FASEB Journal*. 2012;26(8):3493-3502. doi:10.1096/fj.12-208868
19. 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*. 2012;15(6):848-860. doi:10.1016/j.cmet.2012.04.019
20. Chaix A, Lin T, Le HD, Chang MW, Panda S. Time-Restricted Feeding Prevents Obesity and Metabolic Syndrome in Mice Lacking a Circadian Clock. *Cell Metab*. 2019;29(2):303-319.e4. doi:10.1016/j.cmet.2018.08.004
21. Satoh Y, Kawai H, Kudo N, Kawashima Y, Mitsumoto A. Time-restricted feeding entrains daily rhythms of energy metabolism in mice. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2006;290(5):R1276-R1283. doi:10.1152/ajpregu.00775.2005

22. Sun S, Hanzawa F, Umeki M, Ikeda S, Mochizuki S, Oda H. Time-restricted feeding suppresses excess sucrose-induced plasma and liver lipid accumulation in rats. Aguila MB, ed. *PLoS One*. 2018;13(8):e0201261. doi:10.1371/journal.pone.0201261
23. 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*. 2020;31(1):92-104.e5. doi:10.1016/j.cmet.2019.11.004
24. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. *Cell Metab*. 2018;27(6):1212-1221.e3. doi:10.1016/j.cmet.2018.04.010
25. Lowe DA, Wu N, Rohdin-Bibby L, et al. Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men With Overweight and Obesity. *JAMA Intern Med*. Published online September 28, 2020. doi:10.1001/jamainternmed.2020.4153
26. Ravussin E, Beyl RA, Poggiogalle E, Hsia DS, Peterson CM. Early Time-Restricted Feeding Reduces Appetite and Increases Fat Oxidation But Does Not Affect Energy Expenditure in Humans. *Obesity*. 2019;27(8):1244-1254. doi:10.1002/oby.22518
27. Gill S, Panda S. A Smartphone App Reveals Erratic Diurnal Eating Patterns in Humans that Can Be Modulated for Health Benefits. *Cell Metab*. 2015;22(5):789-798. doi:10.1016/j.cmet.2015.09.005
28. Martens CR, Rossman MJ, Mazzo MR, et al. Short-term time-restricted feeding is safe and feasible in non-obese healthy midlife and older adults. *Geroscience*. 2020;42(2):667-686. doi:10.1007/s11357-020-00156-6
29. Bjerre N, Holm L, Quist JS, Færch K, Hempler NF. Watching, keeping and squeezing time to lose weight: Implications of time-restricted eating in daily life. *Appetite*. 2021;161. doi:10.1016/j.appet.2021.105138
30. 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*. 2018;4(4):345-353. doi:10.3233/NHA-170036
31. Tinsley GM, Moore ML, Graybeal AJ, et al. Time-restricted feeding plus resistance training in active females: a randomized trial. *Am J Clin Nutr*. Published online July 3, 2019. doi:10.1093/ajcn/nqz126
32. Lichtman SW, Pisarska K, Berman ER, et al. Discrepancy between Self-Reported and Actual Caloric Intake and Exercise in Obese Subjects. *New England Journal of Medicine*. 1992;327(27):1893-1898. doi:10.1056/NEJM199212313272701
33. Schoeller DA. How Accurate Is Self-Reported Dietary Energy Intake? *Nutr Rev*. 1990;48(10):373-379. doi:10.1111/j.1753-4887.1990.tb02882.x
34. Reckwitz A. Toward a Theory of Social Practices: A Development in Culturalist Theorizing. *European Journal of Social Theory*. 2002;5(2):243-263. doi:10.1177/13684310222225432
35. Mcleroy KR, Bibeau D, Steckler A, Glanz K. An Ecological Perspective on Health Promotion Programs. *Health Education & Behavior*. 1988;15(4):351-377. doi:10.1177/109019818801500401
36. Shen Y, Salley J, Muth E, Hoover A. Assessing the Accuracy of a Wrist Motion Tracking Method for Counting Bites Across Demographic and Food Variables. *IEEE J Biomed Health Inform*. 2017;21(3):599-606. doi:10.1109/JBHI.2016.2612580
37. Ponsiglione AM, Amato F, Romano M, et al. Top-Down Detection of Eating Episodes by Analyzing Large Windows of Wrist Motion Using a Convolutional Neural Network. *Bioengineering 2022, Vol 9, Page 70*. 2022;9(2):70. doi:10.3390/BIOENGINEERING9020070
38. Przulj D, Ladmore D, Smith KM, Phillips-Waller A, Hajek P. Time restricted eating as a weight loss intervention in adults with obesity. *PLoS One*. 2021;16(1):e0246186. doi:10.1371/journal.pone.0246186
39. Yancy WS, Shaw PA, Reale C, et al. Effect of Escalating Financial Incentive Rewards on Maintenance of Weight Loss: A Randomized Clinical Trial. *JAMA Netw Open*. 2019;2(11):e1914393. doi:10.1001/jamanetworkopen.2019.14393
40. Fugard AJB, Potts HWW. Supporting thinking on sample sizes for thematic analyses: a quantitative tool. *Int J Soc Res Methodol*. 2015;18(6):669-684. doi:10.1080/13645579.2015.1005453
41. Guest G, Bunce A, Johnson L. How Many Interviews Are Enough? *Field methods*. 2006;18(1):59-82. doi:10.1177/1525822X05279903

18 Schedule of Events

Activity	Telephone Screening [Day -38 to -52]	Baseline visit [Day -38 to –28]	Run-In period ends (No Visit) [Day 0]	4-week Visit [Day 31 +/-14 days]	12-week Visit [Day 91 +/-14 days]
Study team procedures					
Verbal Consent	X				
Informed Consent		X			
Background, Medical History Medications		X			
Questionnaires (e.g., Insomnia)		X			
Height		X		X	X
Weight		X		X	X
mCC app	X				
Actigraph		X		X	X
Randomization			X		
TRE questionnaire				X	X
Semi-structed WebEx interview					X
Body Composition assessments					
Bioelectrical Impedance Analysis		X		X	X