Influence of time-restricted eating (TRE) on circadian regulation of glucose homeostasis and mitochondrial function — The TIMET Study

NCT04057339

DECEMBER 2, 2021

University of California, San Diego
Consent to Act as a Research Subject

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Who is conducting the study, why you have been asked to participate, how you were selected, and what is the approximate number of participants in the study?
Dr. Pam Taub, M.D. is conducting a research study in collaboration with the Dr. Satchidananda Panda, PhD at the Salk Institute to measure the health impact of a dietary intervention known as time restricted eating (TRE) on patients with metabolic syndrome. You have been asked to participate in this study because you are age 18 years or older, you have been identified as having metabolic syndrome, and you have reported that you eat over a period of 12 hours or more.

There will be up to 144 participants at this site; this is the only site participating in the study. Up to 72 participants will be randomly assigned to the standard of care (SOC) group, which will receive standard health and nutritional wellness guidelines. Up to 72 participants will be randomly assigned to the Time-Restricted Eating (TRE) group which will be asked to limit the number of hours they eat in a day to 10 hours in addition to receiving the standard of care health and nutritional wellness guidelines. Randomly assigned means that you nor the study team has control over which group you are placed into. Your chances for being placed in either group is like flipping a coin; there is a 50/50 chance of being placed into either the SOC or the TRE group.

All the clinical testing will be performed at the UCSD Altman Clinical and Translational Research Institute (ACTRI, 9452 Medical Center Drive, La Jolla CA 92037).

The study is being funded by the National Institutes of Health (NIH).

Why is this study being done?
The purpose of this study is to see if reducing the number of hours during which you eat each day will help reduce your levels of glucose (sugar) in the blood, improve other markers of metabolic and cardiovascular health (i.e. lipid levels, inflammation markers, etc), and improve body composition (i.e. percentage of body fat, waist circumference, abdominal fat, etc).

Circadian clocks ("circa" means approximately and "dian" means day) are daily rhythms in physiology and behavior (activity, sleep, eating pattern) that help our body to anticipate and adapt to predictable events in the environment. These rhythms are generated and maintained by biological clocks that are present in the brain and in almost every organ of our body. Remarkably, even in the absence of any real clock or timing information from a device, our body can keep track of time and thereby help us go to sleep and eat at optimum times. However, as we can choose to eat, exercise, and go to sleep at a time that is dictated by our lifestyle, sometimes we do these daily routines at a time of the day when our body clock has not prepared our body for it. When these abnormal daily patterns continue for several weeks or years, it can affect our health in many ways including body weight, sleep and risk for various chronic diseases. These daily patterns are affected by where we live (such as near to the equator vs in high latitudes where winter days are very short), season, our work habits, age and many unknown factors. Particularly, we are interested in evaluating the effect of eating patterns on the circadian clock and health. If you enroll in this

study and are randomized to the TRE group, you will be asked to choose an 8-10-hour time frame for your eating window, meaning you will fast for the remaining 14-16 hours of the day. If you have a baseline eating window of 14 hours or more, your eating window for TRE intervention will be 10 hours. If you have an eating window of 12-14 hours at baseline, your eating window during the TRE intervention will be 4 hours shorter than your baseline. For example, if your baseline eating window is 12 hours, the TRE intervention will be 8 hours of eating and 16 hours of fasting. Eight hours is the shortest eating window and ten hours is the longest eating window that those in the TRE group will adopt. The research coordinator will help you select the window if you are in this group.

What will happen to you in this study and which procedures are standard of care and which are experimental?

At the beginning and end of the study, we will measure your height, weight, body mass index, percent body fat, waist/hip circumference and blood pressure. We will also measure your blood sugar levels continuously for 2 weeks at a time at the beginning and end of the study. We will do this using a continuous glucose monitor which is a device that will be implanted (it will stick onto the skin's surface with a small sensor that will go into the skin). Additionally, we will use a special type of X-ray (Dual energy X-Ray Absorptiometry (DXA)) scan to collect information about your body composition (amount of fat compared to muscle and bones). We will also collect information about the mitochondria (produces energy for cells in the body) with a muscle biopsy. During the study, we will also ask you to use a smartphone application (called myCircadianClock (mCC), developed by the Salk Institute) to keep track of what you eat, and a wrist-worn actigraphy device (similar to a standard wristwatch) which will monitor your physical activity levels and sleep. By consenting to this study, you are also consenting to use mCC app and also allowing the mCC app/Salk research team to share data with our team at UCSD.

During the study, you will be asked not to adjust the dosage of or start certain types of medications, specifically those affecting blood pressure, cholesterol, and blood sugar, unless recommended by your doctor. If such a change occurs, we ask that you inform us of the change as soon as possible.

All of the following procedures are experimental. If you enroll in this study, the following will take place as part of the study.

A. Visit 1: You will be asked to come to the ACTRI in La Jolla in a fasting state for initial assessment and blood work.
    a. We will measure your height, weight, body mass index, waist and hip circumference, and resting blood pressure.
    b. We will also obtain blood tests by standard vein puncture with a needle.
    c. You will be implanted a continuous glucose monitor on one of your upper arms, and you will be fitted with the wrist-worn actigraphy device (similar to a wrist-worn watch). You will wear both for 2 weeks.
        1. This step will not take place if your labs are not recent enough for us to determine your eligibility for the study. In this case, all other procedures will occur at this visit, but the watch and CGM will not be applied until your lab results have been reviewed and confirm your eligibility. Then, you will be asked to return to the ACTRI for the watch and CGM and your baseline period will begin at this time.
    d. You will then be provided with instructions for installing and using a smartphone application which you will use during the study to record your dietary intake.

e. You will also be asked to complete general health and sleep questionnaires.
f. This visit will take 1-1.5 hours.
g. You will receive $50 for this visit.

B. Visit 2: You will be asked to come to the ACTRI in a fasted state for a muscle biopsy and DXA scan.
   a. You will be asked to undergo a muscle biopsy on one of your thighs.
   b. You will be asked to undergo a full-body DXA scan. The DXA scan will provide us with information about your body composition, such as how much fat, muscle, and bones are in your total body, arms, legs and trunk, abdomen and hip. Changes in the above-mentioned body composition will be documented over the course of the study.
   c. We will review use of the smartphone application again, and answer any questions you may have.
   d. This visit will mark the 2-week baseline screening period, and if still eligible you will be randomized to either the standard of care group or the TRE group.
      - If randomized to the Standard of Care group, you will be given guidelines for healthy eating habits.
      - If randomized to the TRE group, you will also be given guidelines for healthy eating habits, and in addition, you will be asked to restrict your dietary intake to 8-10 hours per day for the next 12 weeks.
      - Both groups will record all dietary intake using the smartphone application.
   e. You will meet with a dietitian at the clinic to discuss dietary expectations (standard of care or TRE) for the study.
   f. After this visit, the 12-week intervention period will be initiated
   g. This visit will take 1.5-2 hours.
   h. You will receive $150 for this visit.

C. Phone Calls: During the 12-week intervention period, you will receive one phone call from the dietitian to check-in with you. This phone call will be 5-10 minutes.

D. Visit 3: After 10 weeks from Visit 2, you will return to ACTRI.
   a. We will implant the continuous glucose monitor on your skin again and ask you to wear the wrist-worn actigraphy device (the device similar to a wristwatch) again for 2 weeks.
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   b. This visit will take 30 min-1 hour.
   c. You will receive $50 for this visit.

E. Visit 4: At the end of the 12-week intervention period, you will be asked to come to the ACTRI for a final visit.
   a. At this visit, you will remove the continuous glucose monitor and the wrist-worn actigraphy device.
   b. We will measure your height, weight, body mass index, waist and hip circumference, and resting blood pressure.
   c. You will be asked to complete the same general health questionnaires from Visit 1.
   d. We will also obtain blood tests by standard vein puncture with a needle.
   e. You will be asked to undergo a muscle biopsy on one of your thighs.
   f. You will be asked to undergo a full-body DXA scan.
   g. You will meet with a study dietitian for a final check-in.
   h. This visit will take 1-2 hours.
   i. You will receive $150 for this visit.

As indicated above, you will receive a up to a total of $400 compensation for fully completing the study.

F. Blood and muscle samples collected during the study will be stored and investigated for the purposes of the study. Dr. Taub will have solitary control of the stored specimens and will be responsible for deciding how your stored blood and muscle will be used. The specimens will be stored for an indefinite period of time. Additionally, they may also be used for future research regarding new, unforeseen research testing such as biomarkers that test for mitochondrial, neuroendocrine, inflammatory, and/or cardiometabolic health.
    a. These specimens and their derivatives may have significant therapeutic or commercial value. There are no plans to provide a compensation to you for potential commercial values.
    b. If you decide later that you do not want the specimens collected from you to be used for future research, you may tell this to Dr. Taub, who will use her best efforts to stop any additional studies and destroy the specimens that were collected for this purpose.
    c. If, as a result of participation in this study, we obtain information that could significantly affect your health or well-being, we will attempt to inform you of the existence of this information. You may then decide if you wish to know what we have learned.
    d. Your samples will be stored using a de-identified code, which cannot be linked to you by anyone other than research personnel. Your samples will be stored in a locked unit which can only be accessed by study personnel.
    e. Please note that all future research will be conducted only after the study has been reviewed and approved by the IRB.

    Regarding storing my **blood** samples indefinitely for future, unforeseen use:
    - YES, you may store my blood samples for future research.
    - NO, you may not store my blood samples for future research.

    _____Initials

    Regarding storing my **muscle** samples indefinitely for future, unforeseen use:
    - YES, you may store my muscle samples for future research.
    - NO, you may not store my muscle samples for future research.

    _____ Initials

G. (Optional) If you successfully completed the study, you may be invited to continue participating in optional follow-up visits (once at 6 months and once at the end of one year). We may ask you to return for additional measurements, actigraphy device, CGM, blood work, muscle biopsy, and/or DXA scan if you choose to participate in the follow-ups for the study.

    Regarding participating in optional follow-up visits:
    - YES, I would like to participate.
    - NO, I would not like to participate. / Not applicable.

    _____ Initials

H. (Optional) If you have non-alcoholic fatty liver disease (NAFLD), you may be invited to participate in an additional screening of your liver fat through magnetic resonance imaging (MRI)/ magnetic resonance elastography (MRE). This will occur once at the beginning and once at the end of the study.

Regarding the liver MRI:

- YES, I would like to participate.
- NO, I would not like to participate. / Not applicable.

_____ Initials

I. We will share with you the data we collect. Your lab results will be uploaded to your UCSD electronic medical record as they are obtained from the lab. However, the results from the watch, CGM, DXA, and muscle biopsy data will not be uploaded to your UCSD electronic medical record; we will provide you with email attachments and/or printouts of these upon completion of the study (or upon withdrawal) as to avoid study bias. You will already have access to the app data.

Study Procedure Details

- **myCircadianClock smartphone application (mCC app).**
  - The mCC app was created by and managed by Dr. Satchidananda Panda's lab at the Salk Institute for Biological Studies. It is HIPAA compliant and double-encrypted. Consenting to use and using the mCC app is necessary and critical for participation in the study.
- **Activities.** This study will ask you to perform tasks and respond to surveys.
  - The myCircadianClock app provides personalized insights into how your daily behaviors relate to quality of life, and to help you manage your general health including weight. In general, richer data entered into the app results in more accurate and informative insights.
  - To drive these insights, myCircadianClock will ask you to: Answer survey questions about your health behaviors, log your body weight, record what you eat or drink, log your exercise, and log your sleep as best as you can.
  - The app sends occasional reminders to complete study activities.
  - Educational material will be sent through the app.
- **Sensor and health data**
  - This study can gather sensory data from your phone if you allow it to upon installation.
  - Learn More: myCircadianClock may use the built-in accelerometer in certain phones to passively keep track of physical activity (passive because this happens automatically and you do not need to enter any information). The app interprets accelerometer data as steps taken, or as different intensity levels of activity. The app can also detect when you use the phone to get an independent estimate of your rest or sleep period. You can also sync the app to Apple Health Kit or Google Fit to capture, activity, heart rate, and body temperature data.
  - For these activity measures to be accurate, you should carry the smartphone on your person as much as possible (e.g., in your pocket, or clipped to your waist). For instance, if the phone is left on a desk or in your car when you go for a walk, it will not be able to detect your walking.
  - The app will also use the built in GPS sensor to tag the location only when you log your data. This will help you to track what and where you eat, which may help you adjust your diet. It helps the research to account for any unusual change in your eating or sleeping pattern due to a change in time zone when you travel.

Change in time zones or moving to a different latitude within the same time zone can change the local sunrise and sunset time or local day-length, which can affect your circadian clock for a few days.

- The use of the myCircadianClock app is not intended to evaluate your health and is not a diagnostic test. If you are concerned about any aspect of your health, you should consult with your physician.

- **Data Gathering**
  - Our daily pattern of activity, sleep, and eating changes with season, latitude, work schedule, and travel. Collected data may reveal how daily behaviors affect your quality of life and body weight, and also advance clinical research into Circadian Rhythm.
  - Learn more: myCircadianClock helps you keep track of health behaviors such as diet, activity, sleep and taking your medications or supplements.
  - Data that you share through the app as part of the research study will create an unprecedented large scale database of daily behaviors and health provided by people just like you.
  - Studying this real-world data will help researchers understand how daily behaviors influence health in real life, with a resolution never achieved before. (Traditionally, these studies are done by asking people to recall answers to very long questionnaires on paper).
  - At the same time, myCircadianClock analyzes your data to provide personalized insights into how your daily eating, sleeping and activity patterns relate to your overall health, and can help you maintain a healthy lifestyle. Since the feedback is determined from multiple days of your routine behavior, some of these insights will be accessible in your phone after two weeks of data collection.
  - To improve data collection, the app may send you a reminder and push notifications. If you do not want to be bothered with these reminders, you can turn this option off.
  - By combining a personal app and a research study, myCircadianClock will help explore how the smartphone may be used with new kinds of clinical research in the future.
- **Privacy**
  - The following personal health information will be collected from you by the app: name, gender, age, email address, phone number, country, language, photos of food/beverages you take, activity/exercise record, timestamp of entries, and geographic location data from entries.
  - Your data will be sent to a secure database where it will be separated from your personal identity.
  - We take several steps to protect your privacy and the privacy of your app data.
  - To certify that you consent to participate in the study, we ask you to enter your name and an email address. This allows study investigators to have a record of who participates in the study, and to email you a copy of the signed consent document.
  - Your name and email are only used for the consent process, and are not associated with data collected from the app.

- App-generated data is associated only with a random study code, and this code is used in all future analyses separating it from any personally identifiable information.
- These steps ensure that researchers analyzing the coded study data will not be able to connect it to any individual user.
- 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.
- Study investigators chose Amazon Web Services for this important responsibility because they are a world leader in the secure storage and protection of sensitive data. They have a proven track record of safeguarding and managing potentially sensitive biomedical data in accordance with regulations that govern human research and medical information (e.g., regulations mandated by Institutional Review Boards [IRB] and the Health Information Portability and Accountability Act [HIPAA]).
- We will de-identify your data and use secure computers, but we cannot ensure complete privacy.
- Only Dr. Satchidananda Panda, Dr. Pam Taub and their Research Teams will know the identities of people who participate in the study.
- One potential loss of privacy would be if someone sees your data from myCircadianClock on your smartphone.
- For security, myCircadianClock suggests that your smartphone be protected either by a passcode or fingerprint sensor. This ensures that only you can enter and use the app.

- **Utilizing Data**
  - Your coded data will be used for research and may be shared with other researchers.
  - Study investigators will analyze coded (no personal identifiers) app data from everyone who agrees to participate in the myCircadianClock study, but they will be unable to connect it back to any individual user.
  - The results of this research may be published in a scientific or medical research journal so that others can learn from this study. Results will never be published in a way that would allow data to be associated with individual users.
  - After this study is completed, other researchers may request access to the coded study data (already stripped of personal identifiers), so that it can be analyzed in a new way to benefit medical research. Those requesting data must agree to use the data for research responsibly and in accordance with applicable regulations; these data requests will be reviewed by a group of study investigators. Amazon Web Services will have no oversight over future research conducted with coded study data.
  - Other researchers who are granted access to coded study data will not be able to connect the data back to study participants.
  - Study data will never be sold to any third party.
- **Issues to Consider**

- Your participation in this study will take 5-10 minutes per day on average. Entering information and responding to surveys should take on average 2-3 minutes each day. Occasionally, tasks may take a few minutes longer (e.g., a longer questionnaire).
- Some questions may make you uncomfortable. Any information you provide is completely up to you. You can decline to answer survey questions or participate in the app's tasks. If a survey question makes you feel uncomfortable, you are free to leave questions blank.
- Participation in this study does not require you to change anything related to your smartphone account or data plan. However, your phone must have data or wifi capability and must connect to internet in order to transmit data to our servers. The app can use either an existing mobile data plan or Wi-Fi connections: you may configure the app to use only Wi-Fi connections if you wish to limit impact on your data usage.

- **Safety and Legality**
  - As with any smartphone app, follow prevailing laws about when and where you use your smartphone. Similarly, follow local and federal regulations about the usage of a smartphone in specific areas.
  - Additionally, the app should not be used in any capacity to perform or document illegal activity. The Salk Institute for Biological Studies, Dr. Satchidananda Panda and all members of his research team, including collaborators, are not liable for any illegal activity that is performed, captured, or stored by the myCircadianClock app.
- **Re-contacting:** You may be randomly selected for contact by the authorized researcher via email or phone to verify your identity or clarify some of your answers to surveys.
- **Study Survey**
  - Some of the tasks in this study will require you to answer survey questions about various health and lifestyle factors.
  - myCircadianClock will collect some of its data on your health behaviors through short survey questions, such as: Did you forget to eat breakfast today? When did you wake up this morning? Do you feel sleepy during the day?
  - Occasionally, there will also be longer surveys that evaluate aspects such as your work habits, quality of life, and sleeping pattern.
  - For dietary information, myCircadianClock will prompt you to take pictures of every food, beverage, water, medication, and supplement(s) you take.
  - When picture taking is difficult or socially awkward as in a meeting, if you forgot to take picture or you are repeatedly eating the same item, you can also enter the information textually from a different screen.
  - In general, more data entered into the app results in more accurate and informative personalized insights.
- **Study Tasks**
  - Some other interactions with the app are designed to maximize both data gathering and the feedback you receive.

- To gather additional information, including but not limited to activity (step counts/distance), heart rate, height and weight, you can sync other smartphone apps and sensory devices (such as Apple Health Kit and Google Fit) with myCircadianClock. You also have the choice to allow the myCircadianClock app to access your location in order to determine the local time. You can allow or deny these features when you first install the myCircadianClock app, and are able to change these settings at any time.
- myCircadianClock will also ask about some information that requires a brief task away from the smartphone, such as: your weight, your height, your waist circumference (occasionally), and your blood pressure. The app also has optional fields to enter relevant results from blood tests and urine samples including: blood glucose, lipid panels (total cholesterol, LDL, HDL, triglycerides), Hemoglobin A1c, Fibrinogen, C-Reactive Protein, Homocysteine, and ketone bodies if you wish to monitor these parameters.
- All data entered is used solely for tracking purposes, not diagnosis. The Salk Institute for Biological Studies, Dr. Satchidananda Panda and his lab are not responsible for providing medical advice and are not liable for the medical care of participants. Participants should contact a medical professional for medical advice.
- The myCircadianClock app provides personalized feedback in the form of graphs and text to display your progress, and provide insights into your health behaviors.
- The app summarizes data about how food, sleep or activity patterns in specific time of the day are associated with your health and wellbeing. These insights may help you understand your health behaviors better, and help you manage your health. Viewing the graphs and text is optional but may be useful or interesting to you.
- For the passive sensing of your physical activity in some phone models to be accurate, it is important to carry your smartphone on your person (e.g., in your pocket, or clipped to your waist). Carrying your phone will also help you log food, beverage, water and activity data as soon as these events occur.
- In your Profile within myCircadianClock, you can set reminders for yourself to complete app activities. In general, more data entered in the app results in more accurate and informative insights.

- **Meals, activity, and sleep:** The smartphone application myCircadianClock (mCC app) will serve as an electronic food, activity, and sleep diary.
  - On the server side, a sub-study dashboard will be created for this specific project. Clinical coordinators from Dr. Taub's research team will have password-protected access to the study data. In the study summary dashboard, the participant's study code and the date of activation of the app will be shown along with their daily log. If a participant fails to log any food data for more than 1 day, the dashboard flags the participant and sends an alert to the coordinator. The coordinators will login to the dashboard at least twice weekly to monitor food intake data, and follow up with flagged participants as necessary.
  - You will self-select an interval of 10 hours per day within which to consume your food. You can easily track your progress of the daily eating pattern with the time-stamping feature of the app that offers a visual summary.

  - If you have any difficulty logging data, or have questions about any of the features of the app, you will be able to contact the study coordinator through the feedback feature of the app. The questions will be delivered to a HIPAA compliant email server specifically set up for this study.
- **Questionnaires**
  - Pittsburgh Sleep Quality Index (PSQI)
  - Munich Chronotype Questionnaire (MCTQ)
  - Beck depression inventory (BDI)
  - Epworth Sleepiness Scale (ESS)
  - Short Form-36 Quality of Life (SF-36)
  - mCC app-related surveys
- **Fasting:** We will ask you to fast for the blood draw and muscle biopsy, which means you will be asked to not consume any food or beverages (except for water) 12 hours prior to your visit
- **Blood draw:** A total of approximately 1 cup (200ml or 16 tablespoons) will be collected from you for the entire study, which is less than what is collected at blood donations. There is the possibility of a blood test being repeated, which would mean the total amount of blood drawn will be more than 1 cup (or 16 tablespoons).
  - A needle or intravenous catheter will be used to draw blood from a vein in your arm at the study visits. An intravenous catheter is a thin, flexible tube that is attached to the needle, which gets inserted into a vein and is held in place with tape. This allows the needle to be inserted only once with the case of multiple blood samplings.
  - We will test for the following with the blood draw:
    - CMP = comprehensive metabolic panel (kidney function, electrolytes, glucose, and liver function)
    - CBC = complete blood count (white and red blood cells (hemoglobin/hematocrit), and platelets ("clotting cells")
    - TSH = thyroid-stimulating hormone (thyroid gland function)
    - HbAa1c= glycosylated hemoglobin (a measure of "average" blood sugar)
    - Insulin= body's response to blood sugar
    - hs-CRP= high sensitivity C-Reactive Protein (a measure of inflammation)
    - Lipoprofile by nuclear magnetic resonance (NMR) = detailed assessment of cholesterol profile with lipid panel
    - Apo B/A = apolipoprotein B/A (a component related to cholesterol and cardiovascular disease development)
  - Blood draws will occur during baseline and at the end of the study.
- **Urine pregnancy test:** Will be performed in women of child-bearing potential (who are still menstruating) at Visit 1 and if positive, will result in exclusion from study participation.
- **Randomization:** Given that you will be randomized to one of two groups, if you are in the standard of care group only, it is unlikely that you will experience the potential benefits of the intervention group (TRE).
- **Continuous glucose monitoring (CGM):** All participants will be implanted with a CGM, and be instructed on its use.

  - You will wear the CGM for one week prior to the start of the 12-week intervention period and for one week before the intervention period ends.
  - The CGM is composed of a quarter-sized sensor that lies on top of the skin and a thin filament that is inserted under your skin.
  - CGM measures the glucose (sugar) in your body by using a sensor that will be placed under your skin. CGMs estimate blood glucose levels with high accuracy that correlates with those obtained from either venous or capillary blood draws.
  - The CGM will be implanted in the following steps:
    - The upper arm area of your choosing will be cleaned with alcohol swabs. The area will be allowed to dry (10-20 seconds).
    - Then, an adhesive (such as SkinTac) will be applied to that clean area. This area will become sticky and tacky (30 seconds-1 minute).
    - The CGM will then be implanted onto the skin through a device applicator that has a needle. The device applicator will be placed on top of the chosen arm area and will be pressed against the skin. This will bring the CGM sensor in contact with the skin and will trigger a needle within the device applicator to release. This needle inserts the thin filament in the superficial layer under the skin. The needle automatically retracts so it will not stay in you. The filament will remain under your skin until the whole CGM is removed. Implanting the CGM takes about 10 seconds.
    - Then, another adhesive tape (such as Rockadex- which is similar to kinesiology tape) will be placed around the CGM on the skin to secure the area.
    - The CGM will then be activated and registered with its reader system.
    - You can go about your normal daily activities (shower, work-out, etc) as it will not interfere with your daily routine.
- **Wrist-worn actigraphy:** This is similar to a wrist watch and it measures activity. It also functions as a wrist watch and will display the time.
  - To measure habitual physical activity and sleep, participants will wear an accelerometer for one week prior to the start of the 12-week intervention period and for one week before the intervention period ends
  - You will be asked to wear this actigraphy watch 24/7 (especially during sleep). As it is water-resistant (not water-proof), you will be asked to take it off when you're submerged in water (showering, swimming, surfing, etc) and to put it back on when you've finished those tasks. You may also remove it if you find that it is causing skin irritations.
  - The actigraphy data will also be used to measure sleep onset, sleep duration and associated parameters (sleep efficiency and sleep fragmentation).
  - You will also complete a short sleep log every morning on the mCC app to record self-reported quality of sleep.
- **Muscle Biopsy:** A biopsy of your leg muscle will be obtained using a special needle.
  - To do a muscle biopsy, an area of skin and the deeper tissues on the outer front portion of either of your thighs will be numbed using anesthetic (xylocaine) and a small (1/4 inch) incision made with a scalpel. There is a chance that a small scar will form. There is also a very small chance that the scars from the biopsy sites may become thick (hypertrophy).

  - The numbing medication, (xylocaine) will be given under the skin to minimize the pain. You may feel some discomfort like a burning or stinging sensation while the anesthetic is being injected under the skin. The risks of using local anesthesia may include temporary numbness, tingling sensations, and potential allergic reaction A very small amount of numbing medication is used so it is very unlikely that you will have any side effects from this medication.
  - The special biopsy needle will be inserted through the incision and into your thigh muscle several times and a small amount of tissue will be removed (about the size of a small pea).
  - After the biopsy is completed, deep pressure will be applied to the site for approximately 20 minutes to reduce the risk of bleeding and then a steri-strip tape will be used to close the incision.
- **Dual Energy X-ray absorptiometry (DXA) scan:** DXA scan will be done using a Hologic discover W densitometer.
  - You will be asked to change into a gown that we will provide. Then, you will be asked to lie supine (lie on your back) on the DXA scan table for 10-15 minutes until the whole-body scan is complete. Then, you will be asked to change into your clothes.
  - As with any form of radiation, there is a carcinogenic or genetic risk. However, the risks are assumed to be minimal as this is a low-energy X-ray modality that uses a low dose to image the body. The total exposure resulting from these imaging studies is calculated to be approximately 0.09000mSv. This amount is less than you would receive from one year of natural exposure in the San Diego area, which is approximately 1.6 mSv. See the section regarding risks below for more details.
- **Magnetic resonance imaging (MRI)/Magentic resonance elastography (MRE):** As an optional part of the study, we will perform an MRI scan (without intravenous contrast) of your liver.
  - You will be asked to change into a gown that we will provide. Then, you will be asked to lie on the MRI scan table for 60 minutes until the scan is complete.
  - A vibrating paddle will be placed over your abdomen
  - We will measure the amount of fat in your liver using these MRI images.

How much time will each study procedure take, what is your total time commitment, and how long will the study last?

Your total time commitment in the study will be about 3.5 months (2 weeks of baseline with 12 weeks of intervention (standard of care or TRE) for a total of 14 weeks). Your total time commitment for each visit will be about 1-2 hours per visit (7-14 hours for all visits).

What risks are associated with this study?

Participation in this study may involve some added risks or discomforts. The risks of this study include:

a) Surveys/Questionnaire: Some questions may make you uncomfortable. Any information you provide is completely up to you. You can decline to answer survey questions or participate in the app's tasks. If a survey question makes you feel uncomfortable, you are free to leave questions blank. Depending on the scores on one

of the questionnaires regarding your mood, you might be asked to complete an interview with a psychiatrist or clinical psychologist to determine to level of your depression. This will also occur if study-staff become concerned that you are at high-risk for suicide based on their conversations with you. If you are found to have significant clinical depression or thoughts of suicide, your referring internist or cardiologist will be notified and you will be referred to appropriate professional treatment for your depression.

b) Smartphone use: As with any smartphone app, use your common sense and follow prevailing laws about when and where you use your smartphone. Just as you would not text while driving, do not interact with the app while driving or doing any other activities which could result in injury. You can always wait until you are in a safe place to perform any app-related tasks.
c) Randomization: Given that you will be randomized to one of two groups, if you are randomized into the standard of care group, you may not experience the potential benefits of the intervention group (TRE).
d) Blood draw
    a. Bruising
    b. Arterial puncture
    c. Pain
    d. Nerve damage
    e. Re-bleeding
    f. Allergy
    g. Blood vessel inflammation, infection, and/or pain
    h. Fainting
    i. Anxiety/fear
e) Wrist-worn actigraphy device: You will be asked to wear a wrist-worn actigraphy device. Despite all the measures taken in material selection, design and manufacturing to ensure biocompatibility, some people may not tolerate wearing the device and can develop skin irritation. If this happens to you, please notify the study personnel immediately. The instructions for use of the watch advise on the measures you can take to limit the chance of experiencing any problems (such as tightness of wearing and regular cleaning).
f) Use of continuous glucose monitor
    a. Redness at the sensor insertion site
    b. Skin irritation (redness, swelling)
    c. Local infection, inflammation, pain or discomfort
    d. Bleeding at the glucose sensor insertion site
    e. Bruising, itching, scarring or skin discoloration, blood clot under the skin, tape irritation, and sensor or needle fracture during insertion, wear or removal.
g) Muscle biopsy
    a. You may also feel some pain in your muscle when the tissue is removed. After the anesthetic wears off, the biopsy site may be mildly tender for 1-3 days. It is likely that a scar may form at the incision site. The scar from the muscle biopsy will be

about 1/4 inch long. There is a very small chance that the scars from the biopsy sites may become thick (hypertrophy).

b. The risks of using local anesthesia may include temporary numbness, tingling sensations, and potential allergic reaction.
c. There is also a small chance of bleeding or infection at the biopsy site.
d. There is a chance fainting could occur during the muscle biopsy.
e. Your muscle will be studied in the laboratory. Some of your muscle may be stored indefinitely and saved for future analysis. A total of two biopsies will be performed, one at the beginning of the study and one at the end of the study. Dr. Taub and her team have performed over 200 muscle biopsies with no complications.

h) Dual energy x-ray absorptiometry (DXA) scan: During your participation in this research study, you will be exposed to radiation from scheduled DXA scans. The total exposure resulting from these imaging studies is calculated to be approximately 0.09000mSv. As with any form of radiation, there is a carcinogenic or genetic risk. However, the risks are assumed to be minimal as this is a low-energy X-ray modality that uses a low dose to image the body. This amount is less than you would receive from one year of natural exposure in the San Diego area, which is approximately 1.6 mSv. Cumulative exposure from radiation may increase your risk of developing certain types of cancer in the future. The principal investigator for this research study has determined and verified that some of the x-rays and/or imaging scans prescribed for this study would typically be performed as part of the standard medical care required to adequately monitor your current illness. If you are especially concerned with radiation exposure, or you have had a lot of x-rays or imaging scans already, you should discuss this with the principal investigator for this study, Dr. Pam Taub , or your regular doctor.

i) Reduced daily feeding period (from ≥ 12 hours per day to 8-10 hours per day)
    a. Hunger
    b. Fatigue
    c. Low blood sugar

j) Inability to start cholesterol-lowering, blood pressure lowering, and blood sugar lowering medications or undergo dose adjustments of these medications during the study period
    a. This could lead to incompletely controlled cholesterol, blood pressure, and/or blood sugar values during the study period which could have either early (e.g. symptoms related to high or low blood pressure, and/or high or low blood sugars) and/or long-term risks (e.g. potentially increasing overall long-term risk of cardiovascular disease/events).
    b. It is advised that you take necessary action in interest of your health; for example- discussing with your primary care provider or postponing the start of the study until you are on stable doses. You may also be withdrawn from the study if medications change and impact study results.

k) Magnetic resonance imaging of liver
    a. Injury/complications associated with the presence of implanted devices or metallic objects which are not compatible with MRI imaging. We will review a

list of MRI Unsafe devices and objects with you prior to your enrollment in the study. You will be excluded from the study if any of these devices or objects are present. Presence of MR Safe devices will be allowed, and MR Conditional devices will be reviewed on an individual patient basis by the principal investigator. Examples of injuries/complications related to the presence certain devices and objects include: device movement, burns, and device malfunction.

b. Anxiety
c. Claustrophobia
d. Discomfort due to loud noise
e. Discomfort due to vibrations of paddle for MRE

l) Unscheduled visits: There may be the possibility of having subjects return for unscheduled visits in between the scheduled visits. This would be for the following reasons: PI discretion, if the bloodwork needs to be redrawn due to lab or processing errors, and/or reapplication of the continuous glucose monitor if it fell off or did not record data.

m) A potential loss of confidentiality. The UCSD Institutional Review Board (IRB), the FDA, and other government agencies may inspect the study records. To minimize the risk of a potential loss of confidentiality, subjects will be assigned a unique subject code and their blood samples will be assigned a different unique specimen code. A separate paper document will link patient identifiers with subject codes and specimen codes. This document will be kept in a secure location in a locked cabinet. Only the PI and study coordinator will have the key to the cabinet. No research documents will have any patient identifiers and will only be labeled with the unique assigned subject codes.

Because this is a research study, there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings. You will be told if any important new information is found during the course of this study that may affect your desire to continue.

What are the alternatives to participating in this study?

This study is optional. You may choose not to participate in this study at any time.

What benefits can be reasonably expected?

There may or may not be a direct benefit to you from this study.

For those randomized into the TRE group, the potential benefit is that by engaging in TRE, you may see overall improvement in cardiometabolic risk factors and decreases and biomarkers, which may improve your overall health and reduce your risk for cardiovascular disease. There may also be improvements in sleep quality and mood.

For those randomized into the standard of care group, you may not experience any benefits.

The potential benefits to society in general include improved understanding of the effects of time-restricted eating on the health of individuals with metabolic syndrome.

Can you choose to not participate or withdraw from the study without penalty or loss of benefits?

Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without penalty or loss of benefits to which you are entitled. If you decide that you no

longer wish to continue in this study, you will be requested to contact the study coordinator and inform the research team of your desire to withdraw from the study. At time of withdrawal, you will be asked to return for final visit(s) involving a wearing actigraphy device, wearing CGM, blood draw, muscle biopsy, and/or DXA scan. You may also be withdrawn from the study if you do not follow the instructions given you by the study personnel. You may be withdrawn from the study if Dr. Taub believes that it is in your best medical interest. You will be told if any important new information is found during this study that may affect your wanting to continue.

Will you be compensated for participating in this study?
In compensation for your time and travel, you will receive up to $400 for fully participating in the study.
Visit 1 - $50
Visit 2 - $150
Visit 3 - $50
Visit 4 - $150

Are there any costs associated with participating in this study?
There will be no cost to you for participating in this study. We will provide free parking for the study visits. We do not provide compensation for cell phones, cell phone data, or Wi-Fi used for the app.

What if you are injured as a direct result of being in this study?
If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at 858-246-4777 for more information about this and to inquire about your rights as a research subject or to report research-related problems.

What about your confidentiality?
Research records will be kept confidential to the extent allowed by law. Your research records will be labeled with a code number. The list that matches your name with the code number will be kept in a locked file in the research team's office. Any research records that identify you will be kept only as paper records in a secure ACTRI location, or as files behind the secure UCSD computer firewall. Any presentations or publications from this information will not identify you. We will collect the following personal health information: name, age, gender, date of birth, medical record number, current and past medical history, list of current medications, and location data from the mCC app. Research records may be reviewed by the UCSD Institutional Review Board, the NIH, the FDA, and the Federal Office of Human Research Protections.

Who can you call if you have questions?
Dr. Pam Taub and/or her research team designee has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Dr. Pam Taub at 858-246-2497 during the day, or call 619-290-1252 (pager) after 5:00 PM.

Principal Investigator (UCSD)	Pam Taub, MD	858-246-2497
Co- Investigator (Salk)	Satchidananda (Satchin)	858-453-4100 ext 1949

	Panda, PhD	
Research Associate (Salk)	Emily Manoogian, PhD	858-453-4100 ext 1077
Study Coordinators(UCSD)	David Van, BS	858-246-2342

A member of our research team is available to answer any questions you may have concerning the application. You can contact them directly through the app or at the following email address: circadian@mycircadianclock.org.

This study is fully funded by grants from the National Institutes of Health (NIH). The investigators have no financial conflicts of interest to disclose. For questions, please contact the research coordinator at 858-246-2510 and she will connect you the appropriate staff at the Conflict of Interest Committee.

Re-contacting. You may also be contacted in the future for study-related follow-up questions and/or to inform you of other research studies you may be eligible for. Please check the boxes below as appropriate.

YES, you may contact me in the future for study-related follow-up	YES, you may contact me about other research studies I may be eligible for	NO, do not contact me about these things after the study ends

Your Signature and Consent

You have received a copy of this consent document and a copy of the "Experimental Subject's Bill of Rights" to keep.

By signing below, you agree to participate in this study.

_____
Subject's name (Print)

_____ _____
Subject's Signature Date

_____
Researcher obtaining consent (Print)

_____ _____
Signature of Researcher obtaining consent Date