ANCILLARY REVIEWS

DO NOT DELETE. Submit the completed checklist below with your protocol.

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB Review***
☐ **Yes** ☒ **No**	Include Gillette resources, staff or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submission**
☒ **Yes** ☐ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org	**Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submission.**
☐ **Yes** ☒ **No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreq@umn.edu* *See: https://policy.umn.edu/research/indide*	
☐ **Yes** ☒ **No**	Require Scientific Review? Not sure? See guidance in the Investigator Manual (HRP-103).	*Documentation of scientific merit must be provided. Contact: hrpp@umn.edu*	
☐ **Yes** ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received prior to IRB approval;**
☐ **Yes** ☒ **No**	Use the Center for Magnetic Resonance Research (CMRR) as a study location?	*Complete the CMRR pre-IRB ancillary review Contact: ande2445@umn.edu*	

☐ **Yes** ☒ **No**	Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?	*Complete the IBC application via eprotocol.umn.edu*	**These groups each have their own application process.**
☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	
☒ **Yes** ☐ **No**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol.* *Contact: privacy@umn.edu*	
☒ **Yes** ☐ **No**	Use data from CTSI Best Practices Integrated Informatics Core? Formerly the AHC Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff* *Contact: bpic@umn.edu*	**Approval must be received prior to IRB approval.** **These groups do not have a separate application process but additional information from the study team may be required.**
☐ **Yes** ☒ **No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.* *Contact: Jenny Pham* *Pham0435@umn.edu*	
☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
☒ **Yes** ☐ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact: kmmccorm@umn.edu*	
☒ **Yes** ☐ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff* *Contact: oncore@umn.edu*	**Does not affect IRB approval.**

PROTOCOL COVER PAGE

Protocol Title	**Time Restricted Eating As a Viable Alternative to Caloric Restriction for Treating Hyperglycemia in a Population with Type 2 (T2DM) diabetes**
Principal Investigator/Faculty Advisor	Name: Lisa Chow, MD, MS
	Department: Department: Medicine, Division of Endocrinology, Diabetes and Metabolism
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Student Investigator	Name:
	Current Academic Status (Student, Fellow, Resident):
	Department:
	Telephone Number:
	Institutional Email Address:
Scientific Assessment	Nationally-based, federal funding organizations
IND/IDE # (if applicable)	N/A.
IND/IDE Holder	N/A.
Investigational Drug Services # (if applicable)	N/A.
Version Number/Date:	V9/2025.03.26

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	03.22.2022	1. We clarified additional measurements we are taking from the V1-3 blood samples. 2. We clarified the procedures involved with getting weekly weights from participants via the wi-fi scale. 3. We noted that the wi-fi scale will be given to the participants at the brief visit following Visit 1, rather than at Visit 1. We wish to make sure the participant is eligible to participate in the study prior to providing them with a wi-fi scale that they can keep.	Yes
2	12.22.2022	1. Upon seeking monitoring services from CTSI, we were informed that the CTSI will not be monitoring our study since we do not meet their monitoring criteria. CTSI does not monitor studies that do not have an IND/IDE/NSR-IDE. We have thus removed language referring to CTSI monitoring. This modification has been made in response to QA Audit RNI00009184. 2. To increase the applicability of the dietary interventions to a broader population, we plan to increase the age criteria from 18-50 years to 18-65 years and remove the 10 years or less duration for diabetes to any duration of diabetes. These 2 changes do not present any safety concerns to our participants.	Yes.
3	04.14.2023	We have expanded our BMI inclusion criteria from BMI:25-35 kg/m^2 to BMI:25-40 kg/m^2	No.
4	03.26.2024	We have expanded the number of participants we may enroll from 100 to 200, and clarified that we anticipate screening 400 individuals of	Yes.

		which 200 will enroll (sign a consent form).	
5	05.03.2024	We will use MyChart as a recruitment strategy for potentially eligible patients of Dr. Chow's colleagues.	
6	10.14.2024	We will recruit from the Endocrinology clinic by providing patients with a QR code that describes the study.	
7	10.21.2024	We will expand the BMI eligibility criteria from 25-40 kg/m2 to 25-45 kg/m2 to facilitate recruitment.	No
8	03.26.2025	We are including the distribution of a flyer to our recruitment strategy.	No

Table of Contents

ABBREVIATIONS/DEFINITIONS

- TRE/time restricted eating
- mCC/My Circadian Clock (mCC)
- CGM/Continuous Glucose Monitoring
- AE/Adverse Event
- T2DM/Type 2 Diabetes

1.0 Objectives

1.1 Purpose: We will perform a feasibility study to test our **overall hypothesis that time restricted eating (TRE) presents a viable alternative to caloric restriction for improving glycemic measures and reducing weight** in overweight/obese patients [BMI:25-45 kg/m^2] with metformin-only treated Type 2 diabetes (T2DM).

If our hypothesis is proven, our research will have the following impact:

• Demonstrate the extent to which TRE is a viable alterative to intentional caloric restriction in improving hyperglycemia while accounting for weight loss

• Demonstrate that TRE is acceptable and sustainable relative to intentional caloric restriction

• Provide critical preliminary data supporting a definitive study of TRE to treat hyperglycemia in T2DM, which would potentially transform current practice and treatment recommendations.

2.0 Background

2.1 Significance of Research Question/Purpose:

Traditionally, hyperglycemia in patients with T2DM is initially treated with metformin, coupled with intentional caloric restriction for weight loss. Sustained weight loss by intentional caloric restriction is difficult. Participation in behavioral-based caloric restriction programs typically reduces total weight by 7-10%, and realistically only 30% of participants achieve this goal. Barriers cited include the need for multiple face-to-face visits, intervention associated costs, and confusion in implementing caloric restriction recommendations.

In contrast, TRE presents a viable alternative to Caloric Restriction. By its simple message and accommodation of dietary preferences, TRE potentially addresses many barriers associated with Caloric Restriction.

2.2 Preliminary Data:

Our preliminary data reported that TRE (8-hour window for 12 weeks) resulted in weight loss (3.7%) while actigraphy-measured physical activity remained unchanged and quality of life improved. Our preliminary data also suggests that TRE is potentially quite acceptable, with 10-hour TRE continued by 60% of participants 16 months later,2 and a ~3.3 kg weight loss still maintained at 36 weeks post TRE intervention.

2.3 Existing Literature:

The effect of TRE on glycemic measures may be more prominent in patients with dysglycemia. Although many studies of TRE on glycemic measures have shown minimal to modest effects; these studies have all been conducted in patients without T2DM. A randomized, crossover study among men with pre-diabetes

(n=8) had shown that 5-weeks of early TRE (with 6-hour eating window, completion of meals at 3 pm) improved insulin sensitivity and beta-cell function compared to 12-hour feeding window; this improvement was independent of weight loss.

There are no published randomized trials comparing TRE with intentional caloric restriction in patients with T2DM.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

Aim #1: Compare the effect of TRE vs Caloric Restriction on glycemic measures: Hypothesis #1: At the end of Supervised-Intervention (Week 12), the TRE group will have similar improvements in Hemoglobin A1c (primary outcome) and other glycemic measures [HOMA-IR, HOMA-B, continuous glucose monitoring] compared with baseline (Week 0) as the Caloric Restriction group.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

Aim #2: Compare the effect of TRE vs Caloric Restriction on weight: Hypothesis #2: At the end of Supervised-Intervention (Week 12), the TRE group will have similar weight loss compared with the Caloric Restriction group as assessed by in-person measured weight.

Aim #3: Compare the effect of TRE vs Caloric Restriction on intervention burden. Hypothesis #3: At the end of Supervised-Intervention (Week 12), TRE will cost less to administer than Caloric Restriction..

Secondary Hypothesis 1.1: At end of Self-Maintained intervention (Week 24), the TRE group will have improved glycemic measures compared with baseline (Week 0) than the Caloric Restriction group.

Secondary Hypothesis 2.1: During Self-Maintained intervention (Week 12-24), the weight trajectory derived from the weekly home-measured weights (wifi-enabled scale) will diverge between the TRE and Caloric Restriction groups, with the TRE group having less weight regain than the Caloric Restriction group.

Secondary Hypothesis 3.1: At Week 12 and Week 24, participants in the TRE group will self-report higher quality of life and intervention acceptance than the Caloric Restriction group.

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description:

For this feasibility study, we will select patients with newly diagnosed/ early-stage patients with T2DM by enrolling patients with metformin-only treated diabetes with relevant demographic information [Age: 18-65 years old, BMI:25-45 kg/m2, HbA1c: 6.5-8.5%, diabetes]. Informed by our preliminary data, we anticipate

screening 400 participants of which 200 will be enrolled. Our goal is 28 participants who completed the study in each group (total n=56).

We will perform a 24-week clinical trial of either TRE with an 8-hour eating window or intentional caloric restriction (Caloric Restriction) where daily caloric intake is reduced by 15%. The study dietitian will meet with the participants weekly (over the phone, Doximity, or zoom) for the first 12 weeks of the intervention (Supervised-Intervention). For the remaining 12 weeks, the participant will maintain their assigned intervention without study dietitian input (Self-Maintained Intervention) to assess intervention sustainability.

4.2 Drug/Device Handling: N/A

4.3 Biosafety: N/A

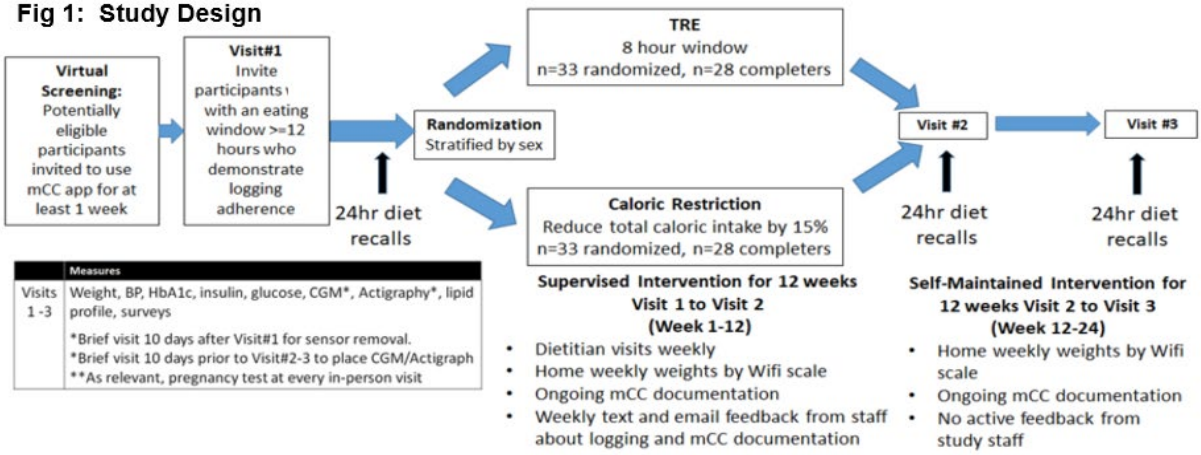
4.4 Stem Cells: N/A

4.5 Fetal Tissue: N/A

5.0 Procedures Involved

5.1 Study Design: Figure 1 shows our study design. The screening visit and Visit 1 will be completed within 1 month. After completion of Visit 1, participants will be randomized to either TRE (8-hour eating window) with *ad libitum* intake or Caloric Restriction (15% reduction of daily caloric intake). Randomization will be stratified by sex. For the Supervised-Intervention (Week 1-12) the study dietitian will meet with the participants weekly (over the phone, Doximity, or zoom); participants will document all food intake using the mCC app and weigh themselves weekly. The effects of Supervised-Intervention will be assessed at Visit 2, which will include in-person labs and weight. Next, the participants will transition to the Self-Maintained Intervention (Week 12-24) where they will continue with the mCC app documentation and weekly weights, with no active feedback from the study dietitian. Visit 3 will assess the effects of the Self-Maintained intervention. Participants will have a brief visit 10 days after Visit 1 to drop off their sensors and a brief visit (10 days preceding) before Visit 2 and Visit 3 to have their sensors placed. As relevant, pregnancy tests will be performed at Visits 1-3 to exclude pregnancy.

Fig 1: Study Design



5.2 Study Procedures:

Virtual Screening Visit: At the virtual Screening Visit, the participants will learn about the study and will be consented. Participants will utilize an institutionally vetted videoconferencing solution (Zoom) available at the University of Minnesota. This consumer friendly, HIPAA-compliant cloud-based platform will allow participants to securely connect with the study team by mobile phone, tablet, or computer.

At the virtual Screening Visit, the participants will also be taught to use the My Circadian Clock (mCC) app, which the study team will help them download (for free) onto their smartphone. Next, the participants will use the mCC app to document their food intake for at least 1 week. Qualified participants will have an eating window (time between 1st food intake and last food take) ≥12 hours and demonstrate logging at least 2 meals ≥5 hours apart for 4 or more days per week.

Similar to our previous work, all participants will have successfully used the mCC app (appropriate logging, established eating window) for at least 1 week before Visit 1. This run-in period will screen out participants who are unable to use the mCC app.

Randomization will occur after completion of the 24 hour dietary recalls, during the brief in-person visit when the sensors are removed (~ 10-14 days after visit 1).

Visits 1, 2, and 3 will occur at the Clinical Research Unity (CRU): Height and weight will be measured. Blood will be drawn in fasting state (at least 8 hours from last-reported non-water intake) to measure HbA1c, blood glucose, hemoglobin (Hgb), insulin, and lipid profile. Creatinine, AST, ALT, and TSH will also be measured at visit 1 for screening purposes. A blood sample from each visit will be stored for future research if the participant agrees to it in the consent form. The Actigraph and CGM will be placed on the participant at Visit 1, and returned by the participant at a brief in-person visit 2 weeks later. Participants will have the Actigraph and CGM applied during a brief visit 10-14 days prior to Visit 2 and Visit 3, and the participants will return the Actigraph and CGM at Visit 2 and Visit 3.

3 brief visits will occur at the Delaware Clinical Research Unit (DCRU). The removal of the sensors that occur 2 weeks after V1 and the placement of the sensors that occur 2 weeks prior to V2 and V3 will occur at the Delaware Clinical Research Unit to accommodate convenient participant parking.

A wi-fi enabled scale will be provided to them at the first brief visit at the DCRU after Visit 1. The participants will be able to keep the wi-fi scale. The coordinator will assist the participants in downloading a free app that is associated with the wi-fi scale. An app account will be set up using a de-identified ID. The participants will weigh themselves weekly using the wi-fi scale until the end of the study (24 times). Weekly weights will be viewed on the app account and entered directly into REDCap.

Surveys:

- **SF-36:** We will conduct SF-36 Quality of Life Survey at Visits 1, 2, and 3.
- **Hunger/Appetite Surveys:** We will use standardized visual analog scales to assess the effects of the interventions on hunger and appetite.
- **Acceptability of intervention:** We will conduct surveys (Visit 2, Visit 3) to assess the participant's satisfaction with intervention, including their views on self-maintenance. Participants will be asked about their perceptions of the intervention's strengths/weaknesses, willingness to continue and willingness to recommend. We will also send follow-up email surveys at 1 and 3 months post-Visit 3 to assess sustainability.

Supervised Intervention Week 1-12:

For the Supervised-Intervention (Week 1-12), all participants document all eating occasions using the mCC app and will have weekly Zoom-based individual counseling session with the study dietitian. In addition, all participants will weigh themselves weekly on the wi-fi scale.

- **Time Restricted Eating (TRE)**

  For the TRE group, each participant will self-select a daily 8-hour eating window. The study dietitian will enter this interval into the mCC app and will instruct the participants to adhere to this eating window during the 24 week intervention. This 8-hour window was established by Dr. Panda and our previous work. During the eating window, participants may eat ad libitum, without restrictions and per personal preference. They should also take their medications that need to be taken with food during this time period. Outside the eating window, only water and medications will be allowed. If a particular medication requires co-administration with food outside the eating window, this will also be allowed. During Supervised-Intervention (Week 1-12), the study dietitian will review the mCC logs

weekly for tailored feedback; this feedback will complement the dietitian's provision of strategies to support maintaining the eating window. This feedback will be given either a virtual visit (by Zoom) or a telephone visit, as per pt preference.

- **Intentional Caloric Restriction (Caloric Restriction)**

  The Zoom-based individual weight loss counseling intervention is based on state-of-the-art behavioral weight loss treatment programs as previously described in the literature. Similar to our current R01, we will have the dietitian create a meal plan using the exchange system. The participant will use the exchange system to achieve the goal 15% reduction of caloric intake. The 15% reduction was selected as recent literature1 suggest that TRE with ad libitum intake reduces caloric intake by ~270 to 300 kcal/day. The 15% caloric restriction is similar to the 11.9% caloric restriction achieved by the CALERIE-2 study.

  All eating occasions will be logged using the mCC app. The study dietitian will review the foods recorded in the mCC app to personalize recommendations. The study dietitian will conduct weekly Zoom-based meetings with the participant during the Supervised-Intervention (Week 1-12). The Caloric Restriction program is based on a conceptualization of effective weight management that emphasizes 1) identifying behaviors in need of change, 2) setting goals for change, 3) monitoring progress, 4) modifying environmental cues to facilitate change, and 5) modifying consequences to motivate change. Session components will include: 1) weekly weighing via wifi-enabled scale; 2) discussion of progress and challenges; and 3) discussion of scheduled session topic. Session content over time includes information on a variety of strategies participants can use to achieve their caloric goals including low energy density choices and recipe modification. Skills required to make appropriate dietary changes will be modeled, practiced, and reinforced throughout the program. To facilitate goal adherence, use of preset menus with associated shopping lists will be encouraged.

Self-Maintained Intervention (Week 12-24): All participants will continue documentation with the mCC app with no active feedback from the study dietitian. In addition, all participants will weigh themselves weekly on the wi-fi scale.

After Visit 3, the dietician will provide complimentary dietary counseling to all participants based on mCC dietary log collected over the preceding 24 weeks. This is to increase study retention through Week 24 of the program.

Procedures:

My Circadian Clock (mCC): The mCC app will be used by all participants to log food and beverage intake for the entire duration of the study. We have used this app with our previously IRB approved study (1701M06001) as well as our ongoing IRB approved protocol (STUDY00008545) This app was designed and is currently maintained by Dr. Panda's group. The app is freely available on the iPhone or Android platform and allows a participant to use the phone camera to take a picture of the specific food or beverage prior to eating. The time stamp and the location are transferred de-identified to a HIPAA compliant data server, which is linked back to the individual by the study team. Participants are randomly reminded (1-2 times per day) to input food intake and cannot view their food record once entered.

We selected the mCC app to assess the eating window and monitor intervention compliance because of its research-orientation. Many commercially-based, consumer-oriented mobile food records (ie. My FitnessPal) are available. However, several reasons limit the research relevance of these commercially-based apps: 1) Unknown validity; 2) Data (e.g. nutrient intake estimates) provision cannot be customized to our needs; 3) Restrictions on data availability for research purposes due to conflicting commercial interests, and 4) Inconsistent rigor with regards to data privacy and security (i.e. not HIPAA compliant). In contrast, the mCC app has been created by Dr. Panda (Co-I) for research purposes, meeting research level requirements (HIPAA compliant, data encryption), full metadata access, and full access for redesigning the software. Many studies, including our own, have used the mCC app.

Sleep and Activity Measurements: We will use the Actigraph Link to quantify physical activity, sleep duration, and sleep quality using actigraphy for a 10 day period at Visits 1, 2 and 3. This accelerometry-based sensor has been used in clinical research to objectively quantify physical activity, sleep duration and efficiency. At Visit 1, we provide the Actigraph Link to the participant (with a brief visit for removal 2 weeks later). Ten days prior to Visit 2 and Visit 3, participants will come in for a brief visit so that the sensor can be applied, followed by removal of the sensor at Visit 2 and Visit 3.

Continuous Glucose Monitoring (CGM): We will use a blinded CGM (Dexcom G6 Pro or Freestyle Pro) to evaluate the intervention's effect on the daily glucose profile (similar to our previous work) for a 10 day period at Visits 1, 2 and 3. The CGM will be applied to the participant at Visit 1 (Brief visit for removal 2 weeks later) and by a brief visit to apply the sensor 10 days prior to Visit 2 and Visit 3. The CGM measures interstital glucose every 5 minutes over 10 days to characterize the participant's glycemic profile.

24 hour dietary recall: Three interviewer-administered 24-hour dietary recall will be collected at baseline (the two week period immediately following Visit 1), Week 10-12 (the two week period immediately preceding Visit 2) and Week 22-24 (the two week period immediately preceding V3) In total, this will be 9 recalls per

participant. The recalls will be conducted over the telephone by trained and certified University of Minnesota Nutrition Coordinating Center (NCC) staff. The recalls will be unannounced (unscheduled within the measurement period) to minimize measurement reactivity. The NCC staff will be blinded to intervention assignment. The Nutrition Data System for Research, a dietary analysis software program developed by the NCC, will be used to collect the dietary recalls. We will use the multiple-pass interview technique to prompt for complete food and beverage recall and descriptions. Using 24-hour dietary recall data, we will calculate average intake of calories, macronutrients and the Healthy Eating Index score. These results will be compared relative to baseline and between interventions.

Wi-fi scale: We will provide participants with a wi-fi smart scale to conduct the weekly weights at home. They will be able to keep this scale after completion of the study. A free mobile app is associated with the wi-fi scale. This will be downloaded to the participant's smartphone. An app account will be created using a de-identified ID and log in information. When participants weigh themselves at home, the weight will be recorded to the de-identified app account online. The study coordinator can view the weight online using the de-identified ID. They will then enter the weight into REDCap. When the participant has completed the study, they will be instructed to change their app ID and log in information so that it can no longer be accessed by the study.

To address Aim 3, we will measure the staff time involved to deliver the interventions. We will measure intervention session time by having the dietitian record the number of minutes spent preparing as well as the in-session time in the REDCAP database, similar to previous work. We will track the overall intervention staff FTE needed. Interventionist time will be converted to costs by multiplying by an appropriate wage rate, which will be the median salary for interventionists with similar qualifications. Time costs for the interventionist will be varied in a sensitivity analysis, since multiple occupational classes, with varying salaries, could deliver the intervention. In addition to staff time, we will estimate the monthly costs required to provide and maintain the mCC app.

5.3 Study Duration: It is anticipated that study participants will be in the study for approximately 7 months.

5.4 Use of radiation*:* N/A

5.5 Use of Center for Magnetic Resonance Research*:* N/A

6.0 Data and Specimen Banking

With participant permission as noted on the consent, we will save deidentified blood samples for future analysis (not genetic testing); participants can withdraw their consent at anytime. The purpose is to leverage the participant's participation in the study by saving samples for future biomarker analysis which may be predictive of study outcomes.

7.0 Sharing of Results with Participants

7.1 Each participant's individual results will be provided to the specific individual. The results will otherwise be analyzed using de-identified data for presentation at national meetings and publication in relevant journals.

7.2 Sharing of genetic testing: N/A

7.2.1 Disclosure of results: N/A

7.2.2 If returning results to participants: N/A

7.2.3 Future analysis of genotypes: N/A

8.0 Study Population

8.1 Inclusion Criteria: Overweight/obese adults with metformin-only treated T2DM [Age: 18-65 years old, BMI:25-45 kg/m^2, HbA1c: 6.5-8.5%, diabetes]. Self-reported weight must be stable [±5 pounds] for at least 3 months prior to the study. Owns a smartphone.

8.2 Exclusion Criteria: Active or anticipated pregnancy during the study, T2DM treated with medications other than metformin, or presence of eating disorders as noted by screening survey.

8.3 Screening: The screening phone call will introduce the study (see phone script), review study eligibility (including a 5 question survey to screen for disordered eating) and include a verbal consent for fasting.

We will request a waiver of documentation of consent during the phone screening.

The Screening Visit (Visit 0) will be a virtual visit using Zoom or Doximity. Informed consent will be obtained by the study team. The entire consent document will be reviewed, including all study procedures and expectations, risks, benefits, and what volunteering means. Candidates will be given time to read the consent, ask questions, and to take the consent home to review if requested. Height and weight will be self-reported. An eConsent/HIPAA form will be developed in REDCap and provided to potential participants for esignature.

The current UMN consent/HIPAA form will include Salk approved consent language for the mCC app usage. The signed consent/HIPAA form will be applicable for both UMN and Salk procedures. Once the participant has signed the consent/HIPAA form, the mCC app will be downloaded from the iTune Appstore or Google Play appstore. After activation of the app and device ID authentication, the study code cannot be concurrently used with another device. A unique random alphanumeric character string will be used to encode the user

and only that identifier will be used to transmit encrypted data between the device and a HIPAA compliant cloud server.

Once consented using the site consent form and the online app consent form, the subject will be scheduled for their baseline appointment (Visit 1).

At the virtual Screening Visit, the participants will be consented, learn about the study and be taught on mCC app usage. Next, the participants will use the mCC app to document their food intake for at least 1 week. **Qualified participants will have an eating window (time between 1st food intake and last food take) ≥12 hours and demonstrate logging at least 2 meals ≥5 hours apart for 4 or more days per week.**

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

Population / Group	Identify whether any of the following populations will be focus of the research (targeted), included but not necessarily the focus or excluded from participation in the study.
Children	N/A
Pregnant women/fetuses/neonates	N/A
Prisoners	N/A
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	N/A
Non-English speakers	N/A
Those unable to read (illiterate)	N/A

Employees of the researcher	N/A
Students of the researcher	N/A
Undervalued or disenfranchised social group	N/A
Active members of the military (service members), DoD personnel (including civilian employees)	N/A
Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	N/A
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	N/A
Individual or group with a serious health condition for which there are no satisfactory standard treatments.	N/A
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	N/A
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	N/A

9.2 Additional Safeguards, if any, to ensure inclusion is appropriate:

Undervalued/disenfranchised/Active members of the military and DoD employees will not be identified and information will not be collected as to a patient's status. This research does not add risk to this group. We will not

specifically recruit from this population but will not exclude a participant from this population if they volunteer and are eligible for the study.

9.3 If research includes potential for direct benefit to participants, provide rationale for any exclusions indicated in the table above: N/A

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented: We will screen approximately 400 individuals. We anticipate up to 200 of these individuals will be consented (enrolled). Our goal is to have 28 participants who completed the study in each group (total n=56). Qualifying participants will proceed with Visit#1.

11.0 Local Recruitment Methods

11.1 Recruitment Process: Our recruitment strategy will be multimodal, including recruitment through the electronic health record, online advertisement, newspaper, television and radio public interest stories; public service announcements; solicitation of health care provider referrals; direct mailings to potential participants; advertisements; small print media, registration in StudyFinder and Clinicaltrials.gov. A study flyer will also be distributed to some diabetes-related external groups, such as the ADA MN Chapter. If these groups are willing, they will in turn either post the flyer on their website or distribute to their member base.

Based on our success with our current NIH funded recruitment (Chow) we will rely heavily on using the electronic health record (EPIC) for recruitment. The University of Minnesota is a partner of the Fairview Health System which has used EPIC since 2011. As of May 2021, the Fairview EPIC system has 3.3 million living patients, with 19465 research-eligible patients with T2DM treated by metformin alone. This constitutes a pool of ~20000 patients with T2DM who are eligible for study recruitment. Based on our previous experience, we anticipate a 10% response rate to this targeted, recruitment approach.

We will send study invitation letters in batches to potentially eligible MHealth Fairview patients using the Fairview Research Recruitment Services (FRRS). Study staff will only call those individuals who respond to the study invitation letter that they are interested in learning more about the study. After providing more information about the study, if an individual remains interested, a Zoom virtual screening visit will be arranged.

The patients at M Health Fairview – Minneapolis Diabetes & Endocrinology Clinic, where Dr. Chow works, may also be screened for eligibility. A study invitation letter may be sent out by Dr. Chow's faculty colleagues in this clinic as well as Dr. Chow's colleagues in the M Health Fairview practice. As with the general Fairview letters, if

a patient responds that they would like to find out more information, our study staff will call them.

In addition to screening for eligible patients at the Minneapolis Diabetes & Endocrinology Clinic, each patient seen at the clinic will be provided information about this study via a QR code that will be attached to their after-visit summary. This clinic-based recruitment effort will involve several IRB approved studies in Endocrinology. An IRB approved QR code for each study, including our study, will be provided to clinic patients as a part of their after-visit summary.

MyChart messages may also be sent out to potentially eligible patients of Dr. Chow's colleagues. The study coordinator will inform the FRRS of these potentially eligible patients and FRRS will send out the My Chart messages via EPIC who have greed to be contacted for research purposes. From MyChart, patients will be directed to call or email the coordinator if they are interested in learning more about the study. Alternatively, as part of the embedded functionality of MyChart, there are 2 buttons that a patient can click on: the "I'm Interested" blue button or the "No, thank you" orange button. When the patient clicks on the "I'm Interested" button, a notification will be sent to the PI's or coordinator's EPIC In-Basket. The PI or the coordinator will respond to the patient with an EPIC response message inviting them to call or email the coordinator.

If recruitment is challenging, we will engage other Twin Cities health systems, such as HealthPartners or Allina Health Systems, for recruitment and consider expanding to patients with T2DM treated by diet only.

11.2 Identification of Potential Participants: Participants may self refer in response to any public advertisements used, such as posters or social media, or through word of mouth.

The University of Minnesota is a partner of the Fairview Health System which has used EPIC since 2011. As of May 2021, the Fairview EPIC system has 3.3 million living patients, with 19465 research-eligible patients with T2DM treated by metformin alone. This constitutes a pool of ~20000 patients with T2DM who are eligible for study recruitment. Based on our previous experience, we anticipate a 10% response rate to this targeted, recruitment approach. BPIC will identify potential participants by applying the eligibility criteria for the study to the EHR record. The first screen will encompass the most recent 6 months review of the EHR. Subsequent screens will include only the past month review of eligible participants. Patients who have opted out of research in their Epic EHR will be excluded from consideration for participation.

11.3 Recruitment Materials:

Participants may self-refer if they become aware of the study through recruitment materials or word of mouth referrals. [A letter about the study may be sent to potential participants, asking them to contact the study coordinator if they are interested.] Individuals who respond to the recruitment materials will be taken through a phone-screening questionnaire. If following the phone screen the potential participant is eligible and interested, the study coordinator will schedule the screening study visit.

The study may utilize social media accounts such as (Facebook, Twitter, Instagram, independent website, etc.) to create an informative space about research opportunities and information for patients with obesity or prediabetes. Describe materials that will be used to recruit participants.

11.4 Payment: Participant compensation will be tied with retention. For the screening visit, the participants will be paid $15. For each completed study visit, the participant will be paid $50.Total compensation will be $165 for completion of the entire study. Each participant will keep their wi-fi enabled scale, which has an estimated value of $90. Additional retention techniques will include: 1) Upfront notice during phone screening and screening visit about time needed for study commitment (7 months duration) 2) Prorated compensation, 3) Tailoring dietary interventions to improve palatability while remaining within the parameters of the intervention.

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances:

- Stopping rules met
- Participant request
- Per judgement of PI

12.2 Withdrawal Procedures: If the participants want to discontinue their dietary intervention, we will offer the following options in a sequential fashion: 1) Address any limiting factors that may prevent program completion, 2) Move the final assessment sooner to be performed at the time of dropping out, 3) Continue data collection as intensively as possible given the participant's preferences. We will also collect reasons for drop out (i.e. time/duration, transportation, side effects, perceptions of efficacy, interaction with staff) to use as potential covariates in the statistical model. In terms of missing data, results from the last observation carried forward as well as multiple imputation analysis. For the final analysis, intention to treat analysis and per-protocol analysis (analysis in those who completed the protocol) will be performed.

12.3 Termination Procedures:

This will be the same as the withdrawal procedures as previous described.

13.0 Risks to Participants

13.1 Foreseeable Risks: There will be minimal physical risks associated with the study as described in next section. The seriousness of these risks is low. The risks to the subjects arise from using established laboratory techniques (Venipuncture, Actigraph activity monitor, CGMs).

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established

Study Procedure	Risk	Likelihood/seriousness/mitigation
Phone screening	Breach of confidentiality	Low/Low. We will ask questions related to health, fitness, and eligibility for the study. Data will be stored on password protected computer in locked area.
Periods of fasting	Hunger, lightheadedness	Low/Low. This will be kept to less than 24 hrs. Adequate fluids (ie water) will be given to minimize dehydration.
History data	Incidental findings, breach of confidentially	Low/Low. We will exclude subjects if history is clinically relevant.
Venipuncture lab tests	Incidental findings, Transient pain/bleeding/bruising;	High/Low. This is a standard blood draw and total amount of withdrawn blood will be held to IRB guidelines.
CGM	Rash on Skin, irritation to skin from adhesive pads, incidental findings	Low/Low. The CGM results will be blinded to the participant. The goal is to monitor glycemic fluctuations with exercise. If significant hyperglycemia or hypoglycemia is noted after unblinding, the patient and their primary provider will be notified for further evaluation and management.
Actigraphy derived sleep and physical activity data	Rash on Skin	Low/Low. Noninvasive measurement of sleep and activity data by wearing Actigraph Link on wrist for up to 14 days

Dietary Recall	Breach of confidentiality	Low/Low. Study staff will call participants and ask about dietary intake for the last 24 hours. The actual call will be unannounced but within a specified 2 week window. Participant will be aware of the 2 week window. This will occur 9 times during the study.

13.2 Reproduction Risks: N/A

13.3 Risks to Others: N/A

14.0 Potential Benefits to Participants

14.1 Potential Benefits: There are no guarantee of benefits. However, there is potential benefit to the human subjects would be weight-loss with the dietary intervention. Since we are deliberately enrolling obese, insulin resistant humans, their physical health may benefit from any observed weight loss. The subjects are allowed to withdraw from the study at any time per their request or per the judgment of the investigator.

15.0 Statistical Considerations

15.1 Data Analysis Plan:

Generalized linear mixed effects models will be used to evaluate differences between the groups (Caloric Restriction,TRE) in subject specific changes for glycemic measures (Aim#1); weight (Aim#2); quality of life (Aim#3); physical activity, sleep quality, and sleep duration from accelerometer data (Exploratory Aim 2.1); and 24-hour dietary recall data during Supervised-Intervention (Week 1-12) and Self-Maintained Intervention (Week 12-24). We will use similar models to compare differences in acceptability and compliance (Exploratory Aim 3.1) between the groups at the end of Supervised-Intervention (Week 12) and at the end of Self-Maintained intervention (Week 24). These models will capture subject specific changes across the full study period (Week 1-24), Supervised-Intervention (Week 1-12) and Self-Maintained Intervention (Week 12-24).

15.2 Power Analysis:

For this feasibility study, the primary objective is evaluating the non-inferiority of TRE compared to Caloric Restriction on HbA1c during the 12 week Supervised-Intervention (Aim#1) with a secondary objective of evaluating the non-inferiority of TRE compared to Caloric Restriction on weight loss (Aim#2). The sample size was chosen to have adequate power to establish non-inferiority for both outcomes.

In our preliminary data, administrating TRE in patients without T2DM, the weight loss from baseline to 12 weeks was 3.6 kg(1.9) for the TRE group and 1.5

kg(2.4) in the control group, with no improvement in HbA1c. In a very small sample of patients with T2DM in a different study,(Section 3.2.3) the decline in weight and HbA1c from baseline was even more pronounced [weight loss: 7.0 kg(3.1), decrease in HbA1c: 0.93% (0.41)] The effect of lifestyle-based weight-loss interventions (diet and physical activity) among adults with T2DM is highly variable across studies.4 A meta-analysis of lifestyle interventions in patients with T2DM estimated a pooled within-group weight loss of 3.41 kg (95% CI 1.79 to 5.04 kg) among nine studies with intervention duration ranging from 16 weeks to 9 years, and a pooled within-group change in HbA1c of −0.38% (95% CI: −0.67, −0.09%) among six studies with intervention duration ranging from 6 months to 1 year.

While this preliminary data indicates that TRE may, in fact, be superior to Caloric Restriction in increasing weight loss and improving glycemic control among individuals with T2DM, we will conservatively power our study as a non-inferiority study. Using a non-inferiority margin for difference in change in HbA1c from baseline to 12 weeks of 0.3% (80% of the expected effect size for Caloric Restriction compared to control), a 2-sided 95% confidence interval to establish non-inferiority, and assuming a standard deviation in change in HbA1c of 0.4%, a total of 56 patients (n=28 per group) would provide 80% power for the analysis of the primary endpoint. This sample size will also give sufficient power (80%) for establishing non-inferiority with regards to weight loss using a non-inferiority margin for difference in change in weight from baseline to 12 weeks of 1.5 kg (the expected change in weight for patients not receiving an active intervention, and 44% of the expected effect size for Caloric Restriction compared to control), assuming a standard deviation in change in weight of 2 kg.

15.3 Statistical Analysis:

Generalized linear mixed effects models will be used to evaluate differences between the groups (Caloric Restriction,TRE) in subject specific changes for glycemic measures (Aim#1); weight (Aim#2); quality of life (Aim#3); physical activity, sleep quality, and sleep duration from accelerometer data (Exploratory Aim 2.1); and 24-hour dietary recall data during Supervised-Intervention (Week 1-12) and Self-Maintained Intervention (Week 12-24). We will use similar models to compare differences in acceptability and compliance (Exploratory Aim 3.1) between the groups at the end of Supervised-Intervention (Week 12) and at the end of Self-Maintained intervention (Week 24). These models will capture subject specific changes across the full study period (Week 1-24), Supervised-Intervention (Week 1-12) and Self-Maintained Intervention (Week 12-24).

We will evaluate whether weight loss is associated with a larger improvement in glycemic control for individuals assigned to TRE (Exploratory Aim 1.1) by testing the three-way interaction between study visit (categorical value), change in weight (% of baseline value), and treatment assignment in the previously

described mixed effects model. If the three-way interaction is not significant, it will be removed from the model and we will evaluate the impact of TRE on glycemic changes accounting for weight loss.

We will use linear mixed effects models to test the relationship between eating habits and sleep by using the average sleep duration/quality using the Actigraphy-based evaluation period and corresponding average eating habits. We will adjust for treatment effect and/or temporal changes if those effects are identified as significant in the primary analysis of group specific differences in change in sleep measures.

As all participants will weigh themselves weekly, we will investigate temporal trends in weight change using a mixed effects model. This model will be constructed using linear slopes with a change point at the start of the Self-Maintained Intervention. We will test whether weight trajectories (slopes) diverge between the treatment arms during Self-Maintained Intervention by testing the appropriate interaction term in the model.

To compare intervention burden between groups (Aim#3) total intervention time (study staff time) and costs (staff FTE times salary and mCC app costs) will be compared between interventions using t-tests.

We will check data distributions before conducting statistical tests and will transform the data if the normality assumption is not met. Logistic models will be used in place of linear models for binary data. We will include relevant clinical factors into our models (including sex, age) to evaluate their influence on change in weight, glycemic measures and quality of life. Secondary analyses will be performed to examine the association between achieved fasting duration and pre-post change in outcomes. These models will include effects of achieved fasting duration, treatment group, and the interaction between both effects. We will use imputation analysis to account for missing data. Intention to treat analysis and per-protocol analysis will be performed. Analyses will be performed in R or SAS (Version 9.4, SAS Institute. Cary, NC).

15.4 Data Integrity:

1. Rigor: Recruitment of participants will be performed using the defined inclusion/exclusion criteria, with particular efforts devoted towards even distributions of men/women and inclusion of minority populations. Data collected at the initial and final study visits will be entered by research staff into Research Electronic Data Capture (REDCap), which uses a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. Data summaries and quality control checks will be run routinely.

2. Transparency: All data obtained in this project will be de-identified with each study subject receiving a unique study ID number. The de-identified data will be routinely shared among team members and discussed at regular meetings to

evaluate recruitment status and the next step of experiments, analyses, and interpretation of the findings. Results of our studies will be submitted for publication in peer reviewed journals, and NIH requirements for access of manuscripts through PubMed Central will be fulfilled.

16.0 Health Information and Privacy Compliance

16.1 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information and therefore assert HIPAA does not apply.

X☐ I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

☐ An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

16.2 Identify the source of Private Health Information you will be using for your research (Check all that apply)

X☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

X☐ I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☐ I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

☐ Other. Describe:

16.3 Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed.

Only patients who have authorized their participation in research in EPIC and have not opted out of research will be provided by BPIC for us to review for our study recruitment.

16.4 Approximate number of records required for review:

Up to 2.8 million (EPIC EHR records). This will be done by BPIC. Only patients who have authorized their participation in research in EPIC will be reviewed. We anticipate that ~ 2000 records will be referred to us for potential contact for study recruitment.

16.5 Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

☐ This research involves record review only. There will be no communication with research participants.

☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

X☐ Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

This communication will include the following: 1) phone calls, 2) letters, 3) texting and 4) Email. We will communicate with participants via telephone (using a study-specific phone number) for pre-screening, appointment scheduling, appointment reminders, etc. We will also communicate through text message or unsecure email if the participant agrees in writing by signing the GUIDELINES AND CONSENT FOR TEXT MESSAGE CORRESPONDENCE FOR RESEARCH PARTICIPANTS and/or GUIDELINES AND CONSENT FOR UNSECURED EMAIL CORRESPONDENCE FOR RESEARCH PARTICIPANTS.

16.6 Explain how the research team has legitimate access to patients/potential participants:

The research team will be permitted to access sources of private information because all participants will be required to sign a HIPAA waiver at the time of informed consent.

16.7 Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

X☐ In the data shelter of the Information Exchange (IE)

X☐ Store **X**☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

X☐ In REDCap (recap.ahc.umn.edu)

X☐ Store **X**☐ Analyze ☐ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

X☐ In OnCore (oncore.umn.edu)

X☐ Store **X**☐ Analyze **X**☐ Share

X☐ In the University's Box Secure Storage (box.umn.edu)

X☐ Store **X**☐ Analyze **X**☐ Share

X☐ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

MedDerm(\\med.ahc.umn.edu\med)(N:)\Chow Group

X☐ Store **X**☐ Analyze **X**☐ Share

X☐ In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices: 20181216

X☐ Store **X**☐ Analyze **X**☐ Share

X☐ Other. Describe:

Describe in detail the location and whether the data / specimens will be stored, analyzed, or shared, and in what ways.

Indicate if data will be collected, downloaded, accessed, shared or stored using a server, desktop, laptop, external drive or mobile device (including a tablet computer such as an iPad or a smartform (iPhone or Android devices) that you have not already identified in the preceding questions

☐I will use a server not previously listed to collect/download research data

☐I will use a desktop or laptop not previously listed

☐I will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

☒I will use a mobile device such as an tablet or smartphone not previously listed

AHC tablet to input survey data (20181716) at each in-person visit

16.8 Consultants. Vendors. Third Parties.

Electronic data will be shared with our external collaborators using the UMN Box account. We will also use the UMN Box account to store results from our external collaborators. All samples sent to the external collaborators (i.e. electronic information to Dr. Panda) will be sent de-identified. These samples will be analyzed and stored in their laboratories as per their institutional protocol. Results from our external collaborators will be placed into the UMN Box account (as per above) for our analysis.

16.9 Links to identifiable data: There is be a participant unique study ID established in REDCap, which will link participants to the data. This will be used to identify the data with the REDCap data. All shared data will be deidentified.

16.10 Sharing of Data with Research Team Members. Data between study members at the University of Minnesota will be shared by phone, voice mail, U of MN email, BOX, centralized shared drive, and REDCap.

16.11 Storage of Documents: In accordance with NIH policy, all study documents will be maintained for at least 3 years after the study ends and for a longer time if required by University of Minnesota policy. All signed and dated HIPAA authorizations and consent documents that include HIPAA authorizations wil be maintained for at least 6 years after completion of the study.

16.12 Disposal of Documents: After this time period, all research records will be destroyed. Computer files will be deleted and hard copy materials will be discarded in accordance with University of Minnesota policy.

17.0 Confidentiality

17.1 Data Security:

- Training: All study staff will be appropriately trained in data security.

• Authorization of access: Only designated IRB-approved staff will have access to the data.

• Password protection/encryption/physical controls: All data will be stored in REDCap.

• Certificates of confidentiality: Since this study will be funded by an NIH RO1 Grant, we will apply for a NIH Certificate of Confidentiality. All entities that are part of this study will be subject to the requirements of this Certificate.

• Separation of Identifiers: Study staff will keep the mapping of identification code to the identity of the participant in a database protected by two-levels of password protection stored separately from the data on Box.

• A Certificate of Confidentiality is automatically issued by the NIH For this project.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

18.1 Data Integrity Monitoring.

Monitoring will be conducted by study staff and the IRB in accordance with the established monitoring plan. Monitoring events will include the following: Study recruitment, subject compliance with visits, subject accrual, adverse events, stopping rules with regard to enrollment/drop out/missing data/adverse events.

The data for each subject will be entered into a REDCap database. The REDCap database uses a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. REDCap includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL database and the web server will both be housed on secure servers operated by the University of Minnesota Academic Health Center's Information Systems group (AHC-IS). The servers are in a physically secure location on campus and are backed up nightly, with the backups stored in accordance with the AHC-IS retention schedule of daily, weekly, and monthly tapes retained for 1 month, 3 months, and 6 months, respectively. Weekly backup tapes are stored offsite. The AHC-IS servers provide a stable, secure, well-maintained, and high-capacity data storage environment, and both REDCap and MySQL are widely-used, powerful, reliable, well-supported systems. Access to the study's data in REDCap will be restricted to the members of the study team by username and password.

The clinical data will be reviewed weekly by the study team to ensure progress, timely data entry and addressing missing data. The clinical data will also be reviewed monthly by Dr. Chow to double-check proper data entry and missing data.

18.2 Data Safety Monitoring.

Recording of Adverse Event:

At each contact with the subject, the investigator and study staff must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study participation should be recorded and reported immediately.

Reporting of Serious Adverse Events

A serious adverse event is any adverse event that is: 1) Fatal 2) Life Threatening 3) Requires or prolongs a hospital stay 4) Results in persistent or significant disability or incapacity or 5) A congenital anomaly or birth defect. Of note, important medical events are events that may not be immediately life-threatening, but are clearly of major clinical significance and may be a serious adverse event. They may jeopardize the subject, and may require intervention to prevent one or the other serious outcomes noted above.

Adverse Event Reporting Plan:

Reporting of adverse events will follow University of Minnesota IRB requirements. Within 48 hrs of any serious adverse event, a verbal or email report will be made to IRB followed by a detailed written report within 10 business days.

Patient safety officer:

We will have Dr. Amir Moheet serve as the patient safety officer for the study. He will review any adverse events related to the study, independent of the IRB and the clinical trials monitor. His report will be submitted to the IRB. His focus will be to provide independent medical opinion on study associated adverse events.

IRB Notification by Investigators

Reports of all serious adverse events (including follow-up information) must be submitted to the IRB within 10 working days if it falls under the UPIRTSO guidelines. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder

Unanticipated Problems Involving Risk To Subjects or Others (UPIRTSO) Events

Investigators are required to submit a report of UPIRTSO events to the IRB within 10 working days of first learning of the event.

Responsible Individual(s) or Group

Monitoring will be conducted by the PI, IRB and independently (i.e. at least annually as a minimum) by qualified staff of the University of Minnesota's Clinical and Translational Science Institute (CTSI, supported by the CTSA grant awarded in 2018) in accordance with the established monitoring plan.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy:

The study consent form will describe in detail any intrusive, uncomfortable, or unfamiliar questions, procedures, or interactions with researchers or study personnel that the participant will be asked to complete. Furthermore, the study consent form will communicate that it is the participant's right to opt-out of any study procedures or the study as a whole or withdraw from the study at any time and this information will be reiterated and revisited periodically throughout the study in advance of intrusive, uncomfortable, or unfamiliar questions procedures or interactions. Participants will not be compelled or pressured to provide information or specimens or study data that they do not wish to provide.

19.2 Access to Participants*:* Participants have been fully informed of the ways in which their data will/may be used during the informed consent process. The research team has been trained in conducting these conversations and the participants are also assessed for their understanding of consent prior to signing the consent form or initiating any study procedures**.**

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury:

In the event that research-related activities result in an injury, treatment will be provided to the participant (e.g., first aid, emergency treatment, and follow-up care as needed). Care for such injuries will be billed in the ordinary manner to the participant or the participant's insurance company.

20.2 Contract Language: N/A*.*

21.0 Consent Process

21.1 Consent Process (when consent will be obtained):

Consent forms describing in detail the study, study procedures, and risks are given to the participant and documentation of informed consent is required prior to any research procedures via written signatures or esignatures using REDCap. The following consent materials are submitted with this protocol:

Consent will take place via a virtual visit using Zoom or Doximity. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will be given the opportunity to review the consent with family and caregivers and return on a subsequent day to sign the consent and enroll in the study.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. We will use the teach-back method to assess the participant's understanding of the study.

All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with others or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

21.2 Waiver or Alteration of Consent Process (when consent will not be obtained):

We will obtain verbal consent over the phone for subject to be fasting for the first visit.

21.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained):

We will ask the IRB to approve a Waiver of Signed Documentation of Consent for the phone screening to determine eligibility and to explain to the potential participant what will happen during the Virtual Screening Visit.

21.4 Non-English Speaking Participants:

N/A

21.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

N/A

21.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:

N/A

21.7 Adults Unable to Consent:

N/A

22.0 Setting

22.1 Research Sites:

Fairview Health System Electronic Health Record (EHR):

The University of Minnesota is a partner of the Fairview Health System which uses a modern enterprise level EHR (EPIC) since 2011 As of May 2021, the Fairview EHR has 3.3 million living patients, with 19465 research-eligible patients with T2DM treated by metformin alone. This constitutes a pool of ~20000 patients with T2DM who are eligible for study recruitment. Based on our previous experience, we anticipate a 10% response rate to this targeted, recruitment approach

UMMC Central Lab

Blood work, other than saved serum/ plasma samples, will be processed at the UMMC main lab and results faxed to the PI.

Clinical and Translational Science Institute (CTSI), University of Minnesota

The Clinical and Translational Science Institute (CTSI) at the University of Minnesota offers comprehensive research support for clinical investigators, from concept through publication. CTSI supports all stages of the research process, providing research and regulatory support, specialized facilities, and analytical services. Concept and pre-study services include assistance with study design (biostatistical support), protocol and budget development, study population definition (i2b2/SHRINE resources), bioinformatics support, investigational new drug (IND) or investigational device exemption (IDE) application assistance, contract negotiations, institutional committee's approval assistance (IRB, Radiation Safety, Institutional Biosafety, etc.), and clinical trial registration with ClinicalTrials.gov. CTSI also offers educational and training opportunities for new investigators and study coordinators. Strong relationships across the University's

Academic Health Center provide access to extensive expertise and collaborative opportunities. Biological specimen handling, storage and retrieval facilities and software (caTissue) are available within the University.

Dr. Chow will be doing most of her clinical research work at the Clinical Research Unit (CRU), a 16,250 square foot inpatient facility including 10 inpatient beds, 4 outpatient beds, rooms dedicated to glucose clamp studies, rooms for human performance studies with specialized equipment for exercise testing, non-invasive vascular investigation and body composition assessments. The CRU is directly connected to the University of Minnesota Medical Center, Fairview and the office building (Phillips Wangensteen Building) where Dr. Chow has her office.

Implementation staffing (research project managers, research nurses and certified medical assistants, clinical research coordinators, clinical trial monitors, a registered dietitian, laboratory technician, and other specialized technical services) can be provided to the extent needed by the investigator. Trial monitoring, and ongoing regulatory reporting and support are provided. The CTSI provides comprehensive clinical research facilities and support across specialty areas, tailored to the needs of the investigator, to facilitate effective and efficient use of resources without unnecessary duplication.

Nutrition Coordinating Center:

The Nutrition Coordinating Center (NCC) is located in the Division of Epidemiology and Community Health, and occupies about 6,000 square feet of office space. Dr. Lisa Harnack (Co-I) is the Director of the NCC since 2007. The NCC includes office space for staff, telephone calling stations, resource area, training room, and conference rooms. The NCC has developed and maintains a research-quality food and nutrient database linked to computerized interactive interview software, the Nutrition Data System for Research (NDSR). The NDSR is designed primarily for clinical research and epidemiological studies investigating relationships between diet and health. The NDSR dietary data collection and nutrient analysis tool is well recognized in the nutrition research community and has been licensed for use in hundreds of research studies. Clients may also choose to enlist the services of NCC to accomplish some or all of their dietary data collection and processing objectives. The NCC Service Center offers training and certification of dietary interviewers, collection of dietary intake by telephone interview, processing of food records, analysis of menu and recipe data, development of dietary data collection protocols, and customized support services for additional related research needs. The Service Center has provided the aforementioned types of services to hundreds of studies since 1974, including carrying out entry and nutrient analysis of food records obtained via meal observation procedures similar to those to be utilized in the proposed study.

Salk Institute:

Environment. The Salk Institute offers an excellent intellectual environment for the scientific success of its faculty. Dr. Panda's lab is part of the Regulatory Biology Laboratories and is housed in the same floor as the Laboratory of Genetics. The open lab structure of the institute offers constant scientific exchange among researchers and PIs. Open lab design of the Salk Institute fosters persistent interactions among these lab members. Panda lab has ongoing collaborations with several Salk Institute faculty in the field of metabolism, endocrinology, and data science. They include Ron Evans, Marc Montminy, Reuben Shaw, Saket Navlakha, Alan Saghatelian with whom Panda lab has several active collaboration projects. These colleagues and their scientific staffs offer a productive intellectual environment relevant to the success of this project.

Laboratory. Laboratory space for 10 full time researchers furnished with standard laboratory equipment (thermocyclers, benchtop centrifuges, dissecting microscopes, DNA/RNA, protein gel electrophoresis apparatus, heat blocks, water baths, freezers, refrigerators, tissue culture hoods, tissue culture incubators, Q-PCR, FPLC) is available within the department of Regulatory biology at Salk institute.

Clinical. The lab has developed, validated, and deployed the myCircadianClock app for monitoring and intervening human eating pattern. The app is hosted on secured HIPAA compliant Amazon Web Server (AWS). The database and the backend processes communicate with the user's smartphone using double encryption.

Computer. The laboratory has 12 recent model PCs, and 3 Macintosh computers. In addition, shared facilities at Salk include high-end personal computers for image processing, database searches, and modeling. Salk institute's central Research Computing department maintains an extensive data communications network available to all laboratories.

Office. The PI has a 100 sq. ft. office located adjacent to the laboratory; desk with computer are available for staff associated with the project.

Biostatistical Design & Analysis Center (BDAC)

Several SPARC servers (Solaris operating system) and Intel servers (Linux and FreeBSD operating systems) provide application service to the CCBR and the Division of Biostatistics. Access to these applications is provided by more than 100 thin-client (X-servers) desktops. All servers are connected to the Internet. The CCBR machines have more than 20 terabytes of disk storage available. Statistical analysis and data management are the primary applications provided by the servers. Statistical analyses are performed using SAS, SAS/GRAPH, SAS/IML, and

R. Oracle is the primary relational database management system. Various SQL clients are used including SAS, Perl, SQL*Plus, and PHP.

22.2 International Research:

N/A

23.0 Multi-Site Research

N/A

24.0 Coordinating Center Research

N/A

25.0 Resources Available

25.1 Resources Available:

Division of Endocrinology, Department of Medicine, University of Minnesota (Primary location Dr. Lisa Chow, PI, Contact PI)

Office:

The Division of Endocrinology has adequate office space for this project. Each faculty member has an individual office and computer assigned for their use. Modern office equipment such as facsimile machines, photocopiers, postage machine, and mailroom services will be available to this project.

Computer Services:

The Division of Endocrinology is part of the Academic Health Center (AHC) and has AHC support for computer maintenance and centralized backup of computer files.

Clinical and Translational Science Institute (CTSI), University of Minnesota

The Clinical and Translational Science Institute (CTSI) at the University of Minnesota offers comprehensive research support for clinical investigators, from concept through publication. CTSI supports all stages of the research process, providing research and regulatory support, specialized facilities, and analytical services. Concept and pre-study services include assistance with study design (biostatistical support), protocol and budget development, study population definition (i2b2/SHRINE resources), bioinformatics support, investigational new drug (IND) or investigational device exemption (IDE) application assistance, contract negotiations, institutional committee's approval assistance (IRB, Radiation Safety, Institutional Biosafety, etc.), and clinical trial registration with ClinicalTrials.gov. CTSI also offers educational and training opportunities for new investigators and study coordinators. Strong relationships across the University's

Academic Health Center provide access to extensive expertise and collaborative opportunities. Biological specimen handling, storage and retrieval facilities and software (caTissue) are available within the University.

During the clinical study, both inpatient and outpatient adult clinical spaces are available in several facilities. Dr. Chow will be doing most of her clinical research work at the Clinical Research Unit (CRU), a 16,250 square foot inpatient facility including 10 inpatient beds, 4 outpatient beds, rooms dedicated to glucose clamp studies, rooms for human performance studies with specialized equipment for exercise testing, non-invasive vascular investigation and body composition assessments. The CRU is directly connected to the University of Minnesota Medical Center, Fairview and the office building (Phillips Wangensteen Building) where Dr. Chow has her office. The Delaware Clinical Research Unit (DCRU), a 36,750 square foot outpatient facility including separate adult and pediatric oriented facilities: Adult facilities include: 10 exam rooms, 4 consultation rooms, 5 specialized rooms, a metabolic kitchen, sample acquisition room and on-site laboratory. The facility provides 23 free parking spaces for research participants.

Implementation staffing (research project managers, research nurses and certified medical assistants, clinical research coordinators, clinical trial monitors, a registered dietitian, laboratory technician, and other specialized technical services) can be provided to the extent needed by the investigator. A state of the art iDXA for bone density and body composition is available on site. Trial monitoring, and ongoing regulatory reporting and support are provided. The CTSI provides comprehensive clinical research facilities and support across specialty areas, tailored to the needs of the investigator, to facilitate effective and efficient use of resources without unnecessary duplication.

Data for this study will be entered into a REDCap database. The REDCap database uses a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. REDCap includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL database and the web server will both be housed on secure servers operated by the University of Minnesota Academic Health Center's Information Systems group (AHC-IS). The servers are in a physically secure location on campus and are backed up nightly, with the backups stored in accordance with the AHC-IS retention schedule of daily, weekly, and monthly tapes retained for 1 month, 3 months, and 6 months, respectively. Weekly backup tapes are stored offsite. The AHC-IS servers provide a stable, secure, well- maintained, and high-capacity data storage environment, and both REDCap and MySQL are widely-used, powerful, reliable, well-supported systems. Access to the study's data in REDCap will be restricted to the members of the study team by username and password.

Fairview Health System Electronic Health Record (EHR):

The University of Minnesota is a partner of the Fairview Health System which uses a modern enterprise level EHR (EPIC) since 2011. As of May 2021, the Fairview EPIC system has 3.3 million living patients, with 19465 research-eligible patients with T2DM treated by metformin alone. This constitutes a pool of ~20000 patients with T2DM who are eligible for study recruitment. Based on our previous experience, we anticipate a 10% response rate to this targeted, recruitment approach.

Division of Epidemiology and Community Health, School of Public Health, University of Minnesota

(Primary location Dr. Lisa Harnack, Co-I)

Nutrition Coordinating Center:

The Nutrition Coordinating Center (NCC) is located in the Division of Epidemiology and Community Health, and occupies about 6,000 square feet of office space. Dr. Lisa Harnack (Co-I) is the Director of the NCC since 2007. The NCC includes office space for staff, telephone calling stations, resource area, training room, and conference rooms. The NCC has developed and maintains a research-quality food and nutrient database linked to computerized interactive interview software, the Nutrition Data System for Research (NDSR). The NDSR is designed primarily for clinical research and epidemiological studies investigating relationships between diet and health. The NDSR dietary data collection and nutrient analysis tool is well recognized in the nutrition research community and has been licensed for use in hundreds of research studies. Clients may also choose to enlist the services of NCC to accomplish some or all of their dietary data collection and processing objectives. The NCC Service Center offers training and certification of dietary interviewers, collection of dietary intake by telephone interview, processing of food records, analysis of menu and recipe data, development of dietary data collection protocols, and customized support services for additional related research needs. The Service Center has provided the aforementioned types of services to hundreds of studies since 1974, including carrying out entry and nutrient analysis of food records obtained via meal observation procedures similar to those to be utilized in the proposed study.

The Nutrition Coordinating Center was established in 1974, and continues to address the ongoing needs of the nutrition research community. The Center is located on West Bank of the University of Minnesota campus and is a 10 minute drive from Dr. Chow's office.

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