Delish Study: Diabetes Education to Lower Insulin, Sugars, and Hunger

AKA Optimizing lifestyle interventions with mindfulness-based strategies in type 2 diabetes

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Supported by:

The National Center for Complementary and Integrative Health

R33 AT009333

Tool Revision History

Version Number: 1
Version Date: 09/17/18
Summary of Revisions Made:

Version Number: 1.1
Version Date: 11/26/18
Summary of Revisions Made:

1. Revised Consent for Screening to include Craving EMA as well as labs; we have modified the protocol accordingly and attach the copy (Consent for Screening Tests).
2. EMA craving assessment: To better capture late-night cravings and eating, we will send a follow-up text the morning after each day of testing to inquire about craving-related eating that occurred the prior night after the evening survey was completed.
3. LADA risk-factors—per site visit recommendation, we added details regarding the LADA-risk factor assessment and cutoff for GAD-65 testing.
4. Updated schedule of assessments to include health history/medications at 3, 6 and 12 months.
5. Added two brief measures:
    a. 2-item survey to assess use of meditation and yoga at baseline.
    b. 3-item survey to assess use of study-prescribed vs. other diet, as well as use of mindfulness or mindful eating (completed at follow-up).
6. Added details regarding planned use of Keto-Mojo ketone meter, in combination with HeadsUpHealth app, to allow for tracking of ketone and blood glucose data online.
7. We have made a number of edits to the full-study consent form to reflect R33 plans as described (and approved) in Version 1 of the Protocol. In addition, we have clarified which screening steps have already been completed versus will be completed in the future as part of the full-study consent, as well as clarified information on destruction of audio recordings to make consistent with the DSMP.

Version 1.2

Version Date: 5/28/19
Summary of Revisions Made:

To better separate participants into high and low adherence groups for randomization to different intensities of maintenance, we changed the cut-off for ketone levels used to calculate the proportion above and below a target ketone level from $\geq$ 0.3 to $\geq$ 0.5 mmol/L.

Per NCCIH suggestion, we are also changing the ketone cut-point for the outcome assessment as well, from 0.3 to 0.5 throughout the protocol.

Version 1.3

Version Date: 12/17/19
Summary of Revisions Made:

1. Clarified that height is measured at baseline to allow for analyses of weight and weight loss in relation to height.
2. Clarified self-report measures in use, as follows:

a. Removed Control of Eating Questionnaire (CoEQ) and Diabetes Distress Scale (DDS), which are not being administered.
b. Added Salzburg Stress Eating Scale and Highly Sensitive Person (HSP) assessments, which are being used.

3. Craving EMA:
    a. Specified that we are aiming to have participants complete at least 8 of 12 craving EMA assessments; fewer than this constitutes a protocol deviation.
    b. Craving EMA is done at the end of the 3 month intervention period, and counts as the 3 month follow-up, but during the intervention period. To avoid confusion and better match the text description of the timing for the EMA assessments, we have removed the x in the intervention period column in the Schedule of Evaluations table.

4. Clarified that Glucose monitoring is personalized by study MDs for safety monitoring and is not used for data analyses.
5. Randomization: We have clarified that although randomization will primarily be done by Project Director Dr. Moran, this task may be delegated to a research associate.
6. We are submitting a revised full-study consent with optional photoplethysmography (PPG) procedure. Note this optional procedure is not being funded by NIH and thus details are not described in the protocol.

Version 1.4

Version Date: 04/08/20

We made the following overall changes in procedures due to COVID-19, as noted in relevant sections:

1. Plans for group sessions to be held remotely, via video conferencing platform (Zoom), until this is no longer felt to be necessary
2. Plans for conducting consenting and follow-up visits remotely via video conferencing (Zoom) or phone if needed due to COVID-19, including new Schedule of Evaluations table summarizing COVID-related modifications.
3. Plans to potentially combine the screening and baseline blood draws to be obtained at the same time to reduce the number of times participants have to go to a phlebotomy site during COVID-19.
4. Proposed adjustments to analyses to account for change to remote classes.
5. Adding some brief questions to the battery of self-report measures that are collected at 3, 6, and 12 months to assess how the coronavirus pandemic, including shelter-in-place, affects food access, diet adherence and emotional eating triggers; also mindfulness practices in those in the treatment arm.

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PRÉCIS

Study Title

Delish Study: Diabetes Education to Lower Insulin, Sugars, and Hunger

(AKA Optimizing lifestyle interventions with mindfulness-based strategies in type 2 diabetes)

Objectives

R33 Specific Aims: We will randomize 120 persons with diabetes in a 1:1 ratio to a nutrition education alone arm (Ed n=60) vs. a nutrition education with mindfulness-based intervention components (Ed+MBI n=60) arm and follow them for 12 months. After the 12-week intervention, we will re-randomize participants using an adaptive intervention design to receive low, medium, or high intensity maintenance training, depending on level of adherence achieved during the intervention period. We will address the following specific aims:

1. Test the hypothesis that the Ed+MBI arm will have better dietary adherence than the Ed arm.
2. Test whether our proposed behavioral mechanisms (e.g. decreased eating in response to cravings or difficult emotions) predict dietary adherence.
3. Compare randomized arms in the adaptive maintenance intervention design to optimize maintenance phase dosing in future trials.
4. Obtain preliminary assessment of intervention effects on clinical outcomes

Design and Outcomes

This is the second phase of a two-phase study.

Interventions and Duration

Participants will attend 11 to 12-weekly study intervention classes based on their random assignment: either Education alone (Ed, 11 sessions) or Education+Mindfulness (Ed+MBI, 12 sessions). Both groups will learn and follow a carbohydrate restricted (CR) diet, and will participate in maintenance phase activities. If assigned to Ed+MBI, they will also learn and practice mindfulness-based skills.

Sample Size and Population

Target sample enrollment size: 120 in the R33 phase.

1. STUDY OBJECTIVES

Our overall hypothesis is that improved ability to manage food cravings and emotional eating is a key mechanism through which mindfulness-enhancements can improve dietary adherence.

1.1 Primary Objective

Primary outcome: For the R33 phase, the primary outcome will be to compare diet adherence between intervention arms. Our primary adherence outcome measure will be the proportion of ketone measures $\geq$ 0.5 mmol/L.

1.2 Secondary Objectives

Secondary adherence measures: An important secondary adherence measure will be non-fiber carbohydrate consumption based on 24-hour diet recall data. This will be assessed two ways: (1) as a dichotomous outcome ($\leq$ 50 g non-fiber carbohydrate/day or not), and as a continuous variable.

Mechanistic outcome(s): We also aim to further test proposed behavioral mechanisms by which training in mindful eating may improve dietary adherence. For each behavioral mechanism, we will test three questions: (1) Is the proposed mechanism associated with improved dietary adherence? (2) Does mindfulness training improve the proposed behavioral mechanism? (3) Does the proposed mechanism mediate improvements in adherence in the mindfulness intervention arm? The proposed behavioral mechanisms through which we hypothesize training in mindfulness may improve dietary adherence are the following:

- Mindfulness training will reduce **frequency of eating in response to cravings** as a result of enhanced ability to address food cravings. Our key measure of this mechanism is frequency of eating in response to cravings using ecological momentary assessment (EMA).
- Strengthened **executive functioning/decreased impulsivity** as measured by the Delayed Discounting task. As the importance of impulsivity may be modified by the responsiveness to food cues, we will also measure this with the Relative Reinforcing Value of Food (RRVF).

- **Decreased emotion-related eating** as measured by the Coping subscale of Palatable Eating Motives Scale (PEMS).
- **Decreased stress-related eating** as measured by two questions about stress-related eating from the MIDUS study and one additional stress-related eating question.[1] We will also measure overall perceived stress using the Perceived Stress Scale (PSS).
- **Improved resilience** (resumption of dietary adherence) after dietary non-adherence occurs. Our key measure will be the time from a ketone measure of < 0.5 mmol/L to higher levels of ≥ 0.5mmol/L, indicating a return to nutritional ketosis after a period of consuming foods that depress ketosis.

We will also assess preliminary evidence that the mindfulness intervention improves **clinical outcomes**, including:

- Glycemic control, using HbA1c. We view improving HbA1c as the primary clinical outcome that we seek to improve in subsequent studies.
- Fasting glucose
- Homeostatic model assessment (HOMA) index of insulin resistance (computed from insulin and fasting glucose measures)
- Weight

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Type 2 diabetes mellitus (T2DM) is a major public health issue. T2DM is the most costly chronic disease in the United States, with 10% of healthcare dollars spent on T2DM.[2] There are currently about 22 million persons in the United States and about 350 million people worldwide with T2DM.[2,3] Lifestyle modification is a key component of disease management, but achieving long-term adherence to diet recommendations is a central challenge. Diet and exercise can improve glycemic control in T2DM. Lowering glycosylated hemoglobin (HbA1c), a central measure of glycemic control in T2DM, reduces the risk of complications such as nephropathy and retinopathy.[4] The Look AHEAD study, based on the successful Diabetes Prevention Program intervention, is the largest trial of lifestyle interventions in T2DM to date. Participants in the intensive lifestyle intervention arm (relative to the control arm) in this trial lost 8 kg more weight and lowered HbA1c by 0.6% after one year.[5] However, these advantages diminished to a 1.6 kg weight and 0.05% HbA1c difference at the end of the trial (with a median of 9.6 years of follow-up).[6] These weaker long-term benefits highlight the importance of developing sustainable approaches to diet intervention in T2DM.

2.2 Study Rationale

Eating in response to food cravings, defined as intense urges or desires to eat specific foods,[7] emotional eating, and mindless eating pose challenges to adherence to diet recommendations, especially for people with diabetes.[8,9] Efforts to achieve a healthy food environment, including changes in the foods available in one's home and workplace, are an important step in adherence to a healthy diet for T2DM. However, foods that are inconsistent with a healthy diet in T2DM are everywhere. Of packaged foods sold in the United States, 74% have added sugars.[10] Seeing desirable food can trigger spontaneous simulations of eating it, including thinking about the pleasure of eating the food, and can activate brain areas involved in taste and reward as if one were actually eating the food.[11,12] Thus the abundant food cues sets up people for frequent cravings and easy access to highly sweetened foods. Enhanced behavioral strategies that support long-term dietary adherence in T2DM are critically needed not only for management of diabetes but for pre-diabetes and obesity, each of which affect over one-third of adult Americans.[13,14]

Mindfulness skills have the potential to enhance dietary adherence. We address an area NCCIH identifies as a high priority for mind-body intervention research in RFA-AT-16-005: "behavior change to promote healthy behaviors such as healthy eating." Jon Kabat-Zinn developed the Mindfulness-Based Stress Reduction (MBSR) program and describes mindfulness as "paying attention on purpose, in the present moment, and nonjudgmentally, to the unfolding of experience moment to moment." One hypothesized mechanism by which mindfulness may increase long-term dietary adherence is by equipping individuals with the skills to acknowledge and experience food cravings and negative emotions without acting on them and by increasing resilience after temporary lapses in dietary adherence. Mindfulness approaches seek to strengthen abilities to become aware of, tolerate, and adaptively self-regulate uncomfortable sensations (e.g., food cravings) without maladaptive responding (e.g., craving-related eating).[15] Current neurobehavioral models of eating behavior are based on experimental data showing that obese persons respond to pictures of high-calorie foods with greater activation of brain regions hypothesized to mediate motivational effects of food cues.[16] This suggests that heightened sensitivity to palatable food cues may confer greater vulnerability to overeating. Other experimental data show that greater sensitivity to palatable food cues is associated with increased palatable food intake only in persons with lower inhibitory control.[17] These data suggest that strengthening inhibitory control may enhance dietary adherence, and may be especially useful for individuals who are more susceptible to palatable food cues. Mindful awareness of one's own experience, a core focus of mindfulness training, can reduce both impulsive responses to attractive food stimuli and the thoughts that they trigger in experimental situations.[18]

In our theoretical model, mindfulness training directed at eating behavior strengthens the ability to tolerate negative states (e.g., cravings for foods incompatible with one's dietary goals) without enacting maladaptive automatic behaviors (e.g., eating in response to craving), providing a potentially powerful tool for facilitating healthy eating behavior. Given the relations above, we focus on cravings as a primary mechanism for overeating. Our intervention choice, mindfulness, may have the unique ability to help people tolerate cravings and reduce compulsive eating, as our pilot data suggests.

Mindfulness training can also bolster adaptive stress management, and thereby holds the potential to reduce stress-eating, which is associated with poorer metabolic health. People who report stress-eating may be more vulnerable to developing obesity and metabolic syndrome.[1] Mindfulness is associated with lower stress-eating in people with diabetes, cross-sectionally.[9] Our mindfulness-based intervention includes mindful eating training along with MBSR-based stress management components which, taken together, act on stress-eating behavior, as well as eating in response to any negative emotions (emotional eating). Improving stress management skills may also directly influence blood glucose levels in T2DM via improvements in maladaptive neuroendocrine responses, as stress hormone responses counteract insulin thereby increasing blood glucose levels..[19,20] Strengthening adaptive coping responses to stress may also facilitate health behavior such as adhering to medication, diet, and exercise regimens.[21,22]

There are important new challenges in optimizing mindfulness-based interventions for diet change. This proposal builds on our group's study of the effects of including mindfulness-based eating and stress management to achieve weight loss and improve metabolic parameters in persons with obesity, but without T2DM (SHINE). While we found evidence of benefits in weight, lipids, and fasting glucose, we also found variability in participant outcomes by teacher that highlights the need to further optimize the intervention manual/approach.

Carbohydrate restricted (CR) diets can provide an important biomarker (ketone level) for dietary adherence and may improve glucose control in T2DM. Current recommendations from the ADA suggest that a variety of carbohydrate levels may be appropriate for persons with T2DM, including reduced carbohydrate diets.[23] We aim to restrict carbohydrates to approximately 10% of caloric intake, or about 50 g/day in this study for several reasons. This induces a low level of ketone production, which has been termed "nutritional ketosis." This provides an *important biomarker* for dietary adherence that we aim to utilize in this study (See Measures in the Approach section). Unlike diabetic ketoacidosis, nutritional ketosis is a stable metabolic state associated with potential health benefits in persons with T2DM. Several studies suggest that lowering carbohydrate intake to this range can improve glucose control, insulin resistance, plasma triglycerides, plasma C-reactive protein, and body weight. [24-30] For example, in a short-term study conducted in a metabolic ward, 10 overweight persons with T2DM consumed their usual diets for 7 days, followed by a CR diet (21 g/day carbohydrate) for 2 weeks. Participants' mean 24-hour plasma profiles of glucose levels normalized, mean HbA1c decreased from 7.3% to 6.8%, and insulin sensitivity improved by approximately 75% on the carbohydrate restricted diet.[31] Our group has compared a CR diet (< 50 grams/day carbohydrate) to a conventional calorie-restricted diet for T2DM and found a significantly greater improvement in mean HbA1c in those on the carbohydrate restricted diet group (see Preliminary data in Approach for further details).[30]

As in other diet interventions, adherence remains a key challenge. In our diabetes pilot study, we found that with limited long-term behavioral support, by 12-months the improvements in HbA1c had declined -0.2% (-0.8 to 0.4, p = .5; unpublished data). While we considered including different diets in the current study, our primary focus is on the role of mindfulness-based intervention components on dietary adherence. We thus choose to keep the diet consistent across groups, and believe a low carbohydrate diet is a good choice because it offers an effective biomarker of adherence, potential health benefits for persons with T2DM, and clear adherence challenges.

This study includes several key innovations.

1. Our theoretical mechanistic model is novel and highly specific, but with broad significance. Cravings and stress lead to overeating sweets and carbohydrate, which worsen glucose control in T2DM. Our mindfulness intervention is uniquely tailored to focus on regulation of both cravings and stress. This pathway is important in obesity and related disorders, and addiction, and thus has the potential for widespread impact of tailored mindfulness-based behavioral interventions.
2. We measure eating in response to cravings and stress using innovative ecological momentary assessment (EMA) methods. We have developed a novel EMA tool to measure these behaviors in vivo and have over 90% compliance in our pilot studies. EMA methods reduce well-known biases of retrospective reporting in traditional single-administration self-report measures of eating.[32]
    a. We use an innovative biomarker approach to assessing dietary adherence to carbohydrate restriction using blood ketone monitoring. While this measure has been previously used in studies of carbohydrate restricted (CR) diets to monitor adherence to CR (including a study by our group) within a study diet arm, to our knowledge, this study would be the first time ketone monitoring will be used as a biomarker to compare different approaches (i.e., mindfulness versus education only) to achieving dietary adherence.
    b. We use an adaptive intervention design to test optimization of the maintenance phase intervention. Our goal is long-term adherence to health behavior change. Few mindfulness-based interventions (MBI) have examined

long-term maintenance strategies, despite the potential importance. In optimizing a maintenance phase intervention, we believe that calibrating the intervention dose based on how participants are doing may be important. Adaptive intervention designs assign intervention intensity/dose based on how a participant is doing (note that despite similar names and certain parallels. Adaptive intervention designs are a different entity from adaptive clinical trials: In adaptive interventions, therapy is individualized based on decision rules, whereas in adaptive clinical trials, the overall trial protocol is modified in response to accruing trial data.[33] We draw on Sequential Multiple Assignment Randomized Trial (SMART) design methods to test adaptive intervention strategies in the maintenance period.[34]. To our knowledge, adaptive intervention designs have not been tested before in published research on MBI interventions. Testing such approaches to MBI maintenance provides an innovative approach that is well-suited to our particular intervention and will provide an important model for future MBI research

3. STUDY DESIGN

This is the second phase of a two-phase study. After pilot testing in the first phase, this second phase will include employment of an adaptive intervention design in the post-treatment phase to test optimization of the maintenance intervention (i.e. assigning maintenance intensity/dose based on how a participant is doing).

We plan an R33 phase trial in which 120 persons with T2DM will be randomized (using a 1:1 ratio) to education alone (Ed) on following a carbohydrate restricted diet for T2DM, or this same education content with added mindful eating/Mindfulness-Based Intervention components (Ed+MBI). All participants will attend an 11 to 12 week (depending on group assignment) in-person group course held at the UCSF Osher Center, providing education on basic behavioral strategies for diet and physical activity and followed for a total of 12 months, including a 9-month maintenance phase. Note: Due to COVID-19, as of March 10 2020, group sessions were transitioned to remote delivery via the Zoom web-conferencing platform, which is accessible on a smartphone, tablet, or computer. All study participants have a smartphone, as this is an existing inclusion criterion. We will use ecological momentary assessment (EMA) methods to measure eating in response to difficult emotions and/or food cravings. We will use an adaptive intervention design during the maintenance phase. Participants will be divided into high or low adherence groups at the end of the initial 3 month intervention period, based on whether they are above or below the median in adherence as measured by proportion of blood ketone levels $\geq$ 0.5 mmol/L. Participants with high adherence will be randomized to either low or medium intensity maintenance components, whereas low adherence participants will be randomized to either medium or high intensity maintenance components for the remaining 9 months. Maintenance groups will have similar content between participants from the original Ed or Ed+MBI trial arms, but group meetings will be conducted separately to prevent contamination of intervention components. We will test the effect of MBI components on our proposed behavioral mechanisms, and on dietary adherence, as well as preliminary effect sizes on weight and glycemic control. For this phase, assessments will be conducted at 0, 3, 6, 9, and 12 months, with study participation lasting approximately 14 months per participant, and the entire R33 phase lasting 3 years.

Randomization will be done using blocked randomization to ensure approximately equal group sizes, with randomly selected block sizes and will be stratified by BMI (below and above 25, i.e. within normal range vs. overweight/obese). Analysis will be performed blinded to group assignment, study physicians will be blinded as much as possible to group assignment when managing medications, laboratory testing will be performed blinded to group assignment, and self-report questionnaires will be filled out by participants using online questionnaires that minimize potential for introducing interviewer bias. However, neither participants nor frontline study staff managing the participant enrollment and groups will be blinded to treatment arm.

Primary behavioral outcome: For the R33 phase, the primary outcome will be to compare diet adherence between intervention arms. Our primary adherence measures will be proportion of ketone measures ≥ 0.5 mmol/L.

Primary mechanistic outcome(s): Our primary hypothesized mechanism is reduction in **frequency of eating in response to cravings** as a result of enhanced ability to address food cravings with mindfulness training. Our key measure of this mechanism is frequency of eating in response to cravings using ecological momentary assessment (EMA).

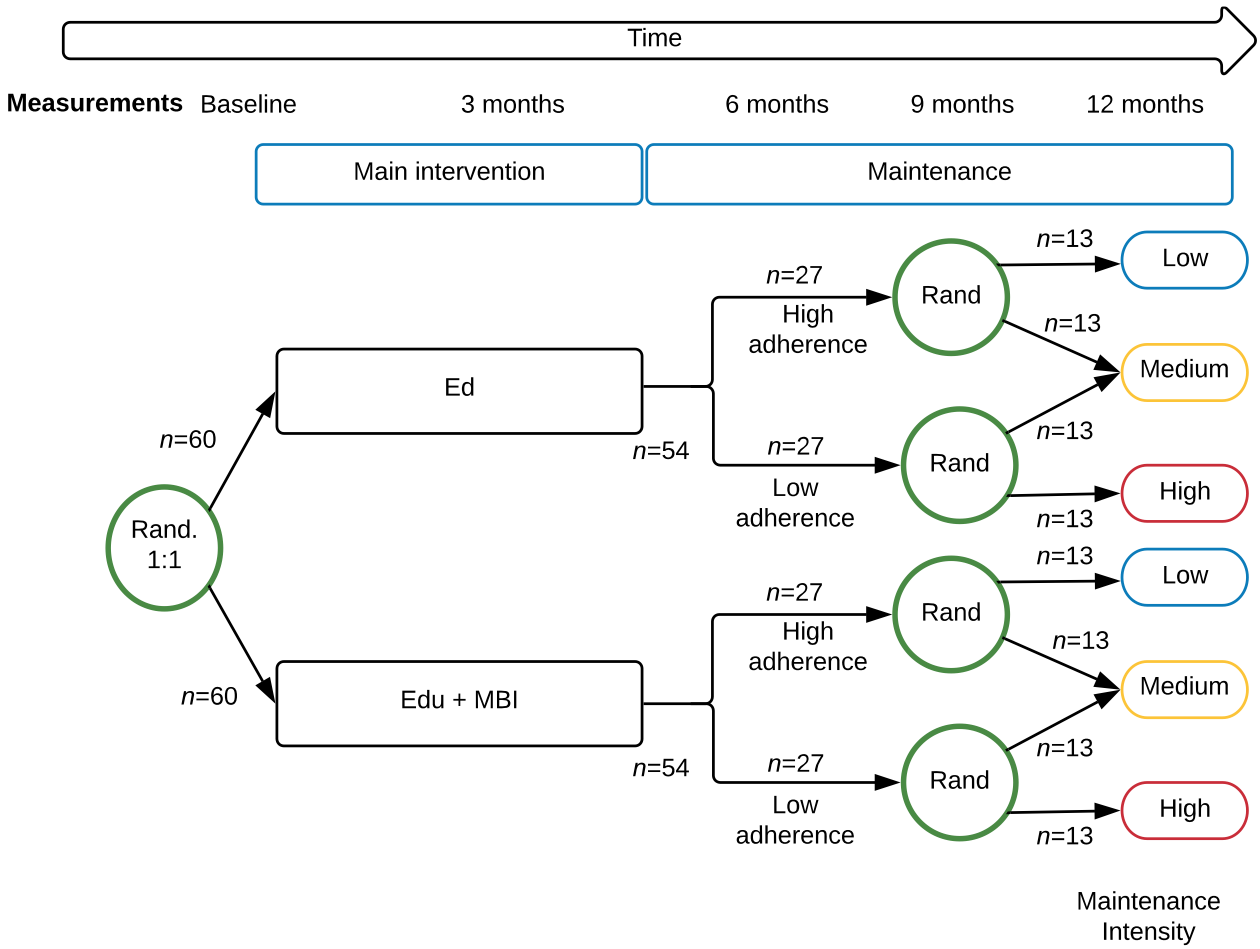


Figure 1: Trial overview. We assume 10% attrition. Participants are randomized a second time at start of maintenance based on diet adherence (above or below the median for proportion of ketone measures ≥ 0.5 mmol/L), into maintenance intensity groups.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Participants must meet all of the inclusion criteria to participate in this study:

1. History of T2DM mellitus. If taking insulin, screening labs will include C-Peptide to rule out T1DM; GAD-65 will be used to rule out latent autoimmune diabetes of adults (LADA). The study intervention is not designed for people with Type 1 diabetes who make no or little insulin.
2. HbA1c ≥ 6.5% and ≤ 12.0% at screening. The lower limit confirms the diabetes diagnosis. Persons with a HbA1c > than 12% typically need immediate attention to the medical regimen, and we aim to have this done before entering the trial to better separate the effects of improved medical regimens from the diet intervention. Potential participants with an HbA1c > 12% can be enrolled once glucose control is improved.
3. Experience food-related cravings most days of the week and eat in response to these cravings regularly. A key hypothesis is that our mindfulness approach will reduce cravings and craving-related eating, and this is primary mechanistic outcome. Thus, we need to recruit participants who experience this.
4. Aged 18 years old and older. We are not enrolling younger children as they may need an intervention that is better tailored to children.
5. Able to engage in light physical activity. We will be recommending physical activity as part of the intervention.
6. Willing and able to participate in the interventions. Must be interested in following a carbohydrate- restricted diet, willing to learn about mindful eating and behavioral strategies for following prescribed diets, have sufficient control over their food intake so that they can follow either diet, and otherwise be able and willing to participate in the intervention. Intervention content must be practiced to evaluate whether it is effective.
7. Have smartphone and are willing to use it on a regular basis for data collection (e.g. craving EMA assessment).
8. Ability to speak English. Groups will be conducted in English, and we do not have the capacity, given the resources available in this proposal, to translate all course material and conduct groups into another language. We enrolled Hispanic participants into the pilot study who were fluent in English, and expect to do this in the proposed study.

4.2 Exclusion Criteria

Candidates meeting any of the exclusion criteria at baseline will be excluded from study participation:

1. Unable to provide informed consent.
2. A substance abuse, mental health, or medical condition that, in the opinion of investigators, will make it difficult for the potential participant to participate in the intervention, that may need immediate changes in medical management that will affect study outcome measures, or that may require important adaptations in the study diet. Such conditions may include cancer, liver failure or cirrhosis, renal failure, untreated hypo or hyperthyroidism, gastroparesis, conditions requiring oral or parenteral glucocorticoid treatment, history of ketoacidosis, or serious bulimia. The study will be conducted in a group setting, and persons with significant substance abuse or mental health conditions that interfere with social functioning in a group setting may be disruptive. Other medical or mental health conditions that need immediate

changes in management, such as thyroid disorders, need to be addressed before starting the intervention so that more reliable baseline measurements can be made prior to beginning the intervention.

3. Pregnant or planning to get pregnant in the next 12 months, breastfeeding or less than 6 months post-partum. The intervention is not designed for the particular diet considerations during pregnancy and breast-feeding.
4. Current use of weight loss medications, such as Alli or amphetamine-based drugs that may affect weight. These treatments may make it difficult to discern the effects of the intervention on outcomes such as weight.
5. Planned or history of weight-loss (bariatric) surgery, or other intestinal surgeries that cause malabsorption. These are likely to change study outcome measures, making it difficult to distinguish the effects of the intervention program, or require extensive tailoring of the diet intervention.
6. Currently enrolled in a weight loss program, such as Weight Watchers or a self-help group such as Overeaters Anonymous, or have unalterable plans to enroll in one of these programs in the next year; using a ketogenic low carbohydrate diet in the past 6 months with advice from a health care professional; or use of a mindful eating program with guidance from a professional in the past 6 months or have ever used the Eat Right Now app. These plans or intervention experience may contaminate study intervention outcomes and/or provide participants with mixed messages about their diet.
7. Vegan or vegetarian. The carbohydrate-restricted intervention diet is more challenging for vegan or vegetarian participants and needs particular tailoring that is difficult to address in adequate detail in a group setting.
8. Unwilling to do regular blood testing at home for glucose or ketone monitoring.

4.3 Study Enrollment Procedures

Identifying and recruiting candidates for the trial entails advertising the study to potentially-eligible participants who will then contact the study for screening and enrollment steps. We will perform outreach based on methods from our previous research. These approaches will be tailored to each of the three main venues at which we plan to recruit: (1) San Francisco General Hospital (SFGH)/SF Health Network: The study team has extensive experience working with the SFGH population. Recruitment in this venue will capitalize on an existing infrastructure for diabetes education. In addition, outreach will be performed at the Diabetes clinic and the General Internal Medicine clinic. (2) UCSF Clinics: We will identify potentially eligible participants through the CTSI recruitment services unit, which reviews electronic medical records and sends patient letters. We have successfully used this service in prior studies. (3) General outreach: This includes outreach through online ads and in local newspapers, posting flyers in public locations, and outreach to community clinicians. Our team has successfully applied these methods in a variety of studies.

Potential participants will make initial contact either by completing the web-based, Qualtrics-powered eligibility screening survey or by calling the study line. Before completing the online study screener, participants will be asked to review the study website as well as the full-study consent (available on the website). They will then complete an online consent to be screened for study eligibility.

Participants who are screened eligible from the Qualtrics screening survey may be asked to watch a video describing study participation and schedule a phone screen to determine initial eligibility. During this call, staff will confirm basic eligibility criteria. The study procedures, including what is involved in participating in the study, as well as the assessment visits will be reviewed with potential participants. The goal is to ensure they understand the commitment involved in study participation.

Those who meet initial criteria and express continued interest in participating will, after providing signed consent (via DocuSign typically) for these steps, complete craving EMA screening and assessment and be provided a lab slip to complete screening labs at LabCorp. Those who do not meet eligibility criteria at any point during the steps to enrollment, including during a phone screen, craving EMA, or screening labs, will be told by study staff that they are not eligible to participate. Those who successfully complete the above steps will come in for an in-person screening and consent visit. The screening and consent visit may be conducted remotely via video conferencing (Zoom) if needed due to COVID-19.

Study enrollment, including reasons for ineligibility at any point along the steps to enrollment or for non-participation of eligible candidates, will be tracked within our study Salesforce database.

Randomization to intervention group and maintenance phase track will be done via the Salesforce database. The randomization table will be programmed by a database manager, who is not otherwise involved in enrollment or other participant procedures. Randomization will be done via the Project Director, Dr. Moran, or delegated research coordinator, who will not have access to the randomization table. When a participant ID number is entered into the database by study staff, a group assignment is revealed. This provides a computerized group assignment that cannot be altered by study staff and the group assigned is immediately recorded in the study database. Randomization will be done approximately 2 weeks prior to the start of classes in order to minimize post-randomization drop-out due to life circumstances that might affect participant ability to attend classes (e.g. such as job loss/change, family emergency, etc.).

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

All participants will attend 11-12weekly study intervention classes based on their random assignment: either Education alone (Ed, 11 sessions) or Education+Mindfulness (Ed+MBI, 12 sessions). Study groups will be held at the UCSF Osher Center for Integrative Medicine; as of March 2020, group sessions will be held remotely, via Zoom webconferencing platform, due to COVID-19, until this is no longer felt to be necessary. Both groups will learn and follow a carbohydrate-restricted (CR) diet for T2DM, and will participate in maintenance phase activities. If assigned to Ed+MBI, they will also learn and practice mindfulness-based skills. Those in the Ed+MBI will start classes one week early, to encourage them to experiment with mindful eating before initiating the low-carb diet, which can significantly alter craving experiences.

Maintenance phase: In the R33 phase, based on the R61 procedures we tested, we plan to utilize three levels of maintenance. Participants will be randomly assigned to maintenance intensity based on ketosis levels at the end of the intervention phase (last 4 weeks). Those with average ketones

above the median for their group will be randomized (1:1) to the Low or Medium intensity maintenance arm; those with average ketones *below* the median for their group will be randomized (1:1) to the Medium or High intensity maintenance arm. If any participants are at the median average ketone level for the last 4 weeks of the intervention period, they will be randomly assigned to above or below the median groups. The various levels of maintenance intensity will include the following elements:

	Low	**Medium**	**High**
Access to archived class materials and resources online	X	X	X
Monthly In-Person or Zoom Meeting (Diet education and, mindfulness instruction for those in Ed+MBI)		X	X
Maintenance survey (regarding adherence to the diet)	none	monthly	biweekly
Follow-up to Maintenance survey call if poor ketone status or help requested	NA	coaching/suggestions by email	coaching/suggestions via phone with diet and/or (if in Ed+MBI group) mindfulness teacher
Medication management	Primarily by PCP, with study-provided medication reduction algorithm. Participants will be told to reach out to study MD if their PCP is not responsive or if they if have more serious concern	By study MDs as indicated	By study MDs as indicated

5.2 Handling of Study Interventions

Intervention content for the Ed program: All participants will receive instruction in the CR diet and basic behavioral strategies in a weekly, in-person (or by Zoom if needed due to COVID-19 precautions), group sessions meeting for 1 to 1.25 hours for 12 weeks. A nutritionist or health professional with experience implementing CR diets with people with T2DM will train participants in how to follow the study diet, utilizing our study manual and curriculum materials developed by the team based on prior studies. The study diet has approximately 10% of kcal coming from carbohydrate, typically 50 grams/day or fewer, not including fiber. Participants will be encouraged to eat a normal amount of protein, typically about 80-100 grams/day (about 20-25% of calories), and

the rest of their calories from fat. Foods that are encouraged include green leafy and other non-starchy vegetables, nuts, seeds, oils (especially olive oil), fish, poultry, tofu, and avocados. Other foods consistent with the diet include berries (in modest amounts), meats, eggs, and cheese. Key foods to minimize include any sugar-sweetened foods or beverages, bread, pasta, potatoes, highly processed packaged foods, and other starchy foods. We have developed extensive materials to educate participants in practical and nutritionally sound approaches to a carbohydrate restricted diet.

Cognitive and behavioral components**:** All participants will receive core behavioral intervention components derived from the Diabetes Prevention Program (DPP),[35] which include goal-setting and self-monitoring of diet.

Intervention content for the Mindfulness program: In addition to the diet components, participants randomized to the Ed+MBI group will receive MBI components using the Eat Right Now (ERN) platform. This will consist of two integrated components: 1) use of the ERN app at home, during the week, to learn and practice mindfulness skills for food-cravings and eating, and 2) in-person (or by Zoom if needed due to COVID-19 precautions) group-based discussions of how the mindful eating practices are going, trouble-shooting obstacles/pain points, and doing group exercises and reflecting on them. The Eat Right Now program provides brief videos of 2 to 6 minutes in length on mindfulness and mindful eating topics. In the R61 phase, participants could watch the video segments for the week at the beginning of in-person sessions each week. Few people took advantage of this option or found it helpful, as the video segments can also be viewed on a smartphone or tablet at home in a self-paced manner. Thus, for the R33 phase, we will not offer this option. Group sessions will be led by an experienced mindfulness instructor with training in mindful eating and familiarity with a CR diet for T2DM, and will focus on discussion of how the mindful eating practices are going, trouble-shooting obstacles/pain points, and doing group exercises and reflecting on them. The Eat Right Now app also includes the audio tracks of meditation exercises are core components of our mindful eating program (e.g. body scan, mindful eating practices) that participants can access at any time – which will allow them to cultivate their mindfulness practice in the context of their daily lives. Twelve one-hour sessions addressing mindful eating will be conducted weekly for 12-weeks (monthly during maintenance), before each diet session. The key content of the mindful eating intervention components focuses on: helping people improve their relationship with food and control food cravings, using mindful eating approaches including: paying attention, noticing habit loops, understanding brain science and food/sugar addiction, disrupting emotional and stress eating, cultivating acceptance and curiosity, learning lovingkindness, detaching from thoughts, using healthy restraint, and maintaining motivation.

Delivery of group sessions via video-conferencing (Zoom): As of March 2020, due to COVID-19, we transitioned group sessions to remote delivery via the video-conferencing platform, Zoom. The content of the sessions is identical to in-person delivery for both the Mindfulness and the Diet components. For both classes, the content and process is the same as in-person sessions except that instead of the participants being with the teacher and other participants in person, they meet virtually. Participants are asked to attend class with video if possible, so that they can see and be seen by everyone else. For the mindfulness class, curriculum and approach is unchanged, with teachers leading guided meditations, doing inquiry, and providing some didactics each session. For the diet class, the teacher continues to provide the same Power-Point presentation, lead discussion, and answer questions with participants. Zoom is a HIPAA compliant web and video conferencing platform

already in use at UCSF for remote medical visits, and with necessary business associate agreement and procedures in place to ensure HIPAA-compliance.

Differences between in-person vs Zoom classes: In both treatment arms, participants miss opportunities for informal interactions that might have previously taken place before and after class. Remote alternative: As we start the Zoom sessions early to provide technological support to participants who might need help, we will allow participants to "arrive early" and if they don't need any technological or other help from staff, they can be placed in a virtual "waiting room" where they can interact informally with others who arrived early.

Other minor differences in the diet curriculum include: 1. Ketogenic snack: During in-person sessions, we served participants a ketogenic snack, in part because many were coming straight from work without time for dinner, but also as a way to introduce people to some new foods and/or give them ideas for snack options. 2. Lending library: For in-person sessions, we made a lending library of ketogenic cookbooks and other books available to participants to check out and read at home. Remote alternative: Provide participants with a list of the books that we had in our lending library and offer to send them one of their choice.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

Participants are allowed to continue on medications prescribed by their physicians, except for those outlined in the exclusion criteria: oral or parenteral glucocorticoid treatment; weight loss medications or supplements such as Alli or amphetamine-based drugs that are believed to effect on weight.

5.3.2 Required Interventions

There are no required supplements or medications for this study.

5.3.3 Prohibited Interventions

As per the eligibility criteria, people utilizing the following interventions will be excluded from the study: current use of weight loss medications or supplements, such as Alli or amphetamine-based drugs that are believed to have an effect on weight; current enrollment in a weight loss program, such as Weight Watchers or a self-help group such as Overeaters Anonymous, or unalterable plans to enroll in one of these programs in the next year; using a ketogenic low carbohydrate diet in the past 6 months with advice from a health care professional; or use of a mindful eating program with guidance from a professional in the past 6 months or have ever used the Eat Right Now app; history of or planned weight loss surgery.

5.4 Adherence Assessment

Our primary measure of adherence to study regimen is attendance at weekly class sessions, defined as proportion of the weekly study intervention sessions attended. We will define good adherence as attending at least 8 of the main sessions. Attendance is tracked by staff at each session, with data entry specifying if attendance was by Zoom.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Screening/ Consent Visit	Baseline Assessments	Randomization	Intervention Period	3 & 6 Month Follow-Up	9 Month Follow-Up	12 Month Follow-Up
Informed Consent	x						
Health History/ Medications	x				x	x	x
Demographics and Background Information	x						
Inclusion/Exclusion Criteria	x						
Craving EMA Assessment	x	x			x	x	x
Blood Draw/Labs	x	x			x	x	x
Online questionnaires/self-report Measures		x			x		x
24-hour diet recall		x			x		x
Cognitive Measures	x				x		x
Weight (all timepoints) and height (baseline only)		x			x		x
Enrollment/Randomization			x				
Diet and/or Mindfulness Education				x			
Ketone monitoring for Dietary Adherence				x	x	x	x
Home glucose monitoring for safety				x			

Schedule of Evaluations –COVID-related modifications

Assessment	Timepoint	COVID-19 modification if/when in-person visits are not possible
Informed Consent	Screening/consent	Consent reviewed w Pt over Zoom, signed via Docusign
Health History/ Medications	Screening/consent, 3, 6, 9, 12mos	Interview done via Zoom or phone (Note: at 9 months, this has always has been done via phone).
Demographics and Background Information	Screening/consent	No change—done via Qualtrics
Inclusion/Exclusion Criteria	Screening/consent	No change
Craving EMA Assessment	Screening/consent, baseline, 3, 6, 9, 12mos	No change
Blood Draw/Labs	Screening/consent, baseline, 3, 6, 9, 12mos	Potential use of blood spot if visits to LabCorp are not advised
Online questionnaires/self-report Measures	Baseline, 3, 6, and 12mos	No change
24-hour diet recall	Baseline, 3, 6, and 12mos	No change
Cognitive Measures	Baseline, 3, 6, and 12mos	2 key tasks will be done remotely; 3 secondary tasks involving reaction time will not be administered if in-person visits are not feasible.
Weight (all timepoints) and height (baseline only)	Baseline, 3, 6, and 12mos	Weight/height measurement will be self-reported by the participant, if possible by a photo of themselves on a home scale (provided by the study, if needed).
Enrollment/Randomization		No change.
Diet and/or Mindfulness Education	3-month intervention phase; 9 month maint-enance phase	Provided via Zoom web-conferencing platform.
Ketone monitoring for Dietary Adherence	Intervention, 3, 6, 9, 12mos	No change.
Home glucose monitoring for safety	Intervention period	No Change.

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Consenting Procedure

A two-step consenting process will be used:

Consent for Screening Tests: Those who meet initial criteria after a phone screen will provide consent for screening steps (craving EMA screening and screening labs), typically electronically via DocuSign.

Full-Study Consent: Those who successfully complete the screening craving EMA and lab steps will come in for an in-person visit, where they will provide written consent for the remainder of the study.

At the first in-person visit, study staff will provide participants a copy of Experimental Subjects Bill of Rights, then review the consent form with the participant. If they are interested, participants will have the consent form and HIPAA form read aloud to them and will have unlimited time to review it on their own carefully. The study staff will verbally outline the important points of the consent form, including that the study is voluntary and they can drop out at any time, that participation or lack thereof of will not affect their medical care, and that all information is kept confidential. The main requirements and inconveniences involved in the study will also be described. They will be informed about physical risks involved. Interested participants will then sign the consent form, the staff person will co-sign it, and a photocopy will be given to the participants to keep if desired.

Written informed consent with the participant will be done by either the Project Director, study coordinator, and/or research assistant. All staff involved in consenting will have completed human subjects CITI training.

Documentation of signed consent will be completed in the study Salesforce database.

COVID19 modifications to consenting procedures: When in-person visits are not allowed or advised, full-study consent will be obtained during a virtual visit conducted via Zoom, and participants will provide Docusign consent for the remainder of the study. Prior to this Zoom visit, participants will be emailed copies of the consent form as well as the Experimental Subjects Bill of Rights to review. During the Zoom visit, study staff will review the Experimental Subject Bill of Rights with the participant, then review the consent form with the participant, as has been done during in-person consent. As with in-person procedures, staff will verbally outline the important points of the consent form as described above. Interested participants will Docusign the consent form, and staff will co-sign it; a copy of the signed consent form will be emailed to the participant if desired.

Screening

Online screener: Interested potential participants will visit the study website, which will consist of the IRB-approved study flier, with link to consent form and online screener. After completing online consent to be screened, they will complete a questionnaire to screen for initial eligibility of the following:

- T2DM, HBa1c within range, experience food cravings and craving-related eating, willing and able to participate in the interventions (including diet and mindfulness components, schedule allows for class attendance and study visits), able/willing to use own smartphone for study procedures; excluded substance abuse, mental health, medical conditions, or medications; 18 years or older, able to engage in light physical activity, English-speaking, pregnancy-related exclusions; weight-loss medications, programs, or surgery exclusions; vegan or vegetarian; unwilling to do home monitoring.

Phone screen: Study staff will review completed online screeners and may invite those who appear to be potentially eligible to watch a study recruitment video (describing participation commitment), then complete the phone screen to confirm and further assess eligibility and discuss questions a participant may have.

Consent for screening tests: Those who pass the phone screen will be asked to complete the craving EMA and labs screening steps, after providing consent for these procedures:

> *Craving EMA:* This step provides confirmation of food-craving and craving-related eating criterion. If this step is completed more than 4 weeks before the class start date, it will be repeated for baseline assessment prior to randomization.
>
> *Screening labs:* Those who pass the phone screen will be given a requisition to have fasting screening labs done at a LabCorp convenient to them. Screening labs include: Hba1c in range; TSH in normal range, and normal liver and kidney function. If a potential participant is on insulin, C-peptide will be used to rule out T1DM; GAD-65 will be used to rule out latent autoimmune diabetes of adults (LADA) in those with two or more LADA risk factors (i.e. age younger than 50 and/or BMI lower than 25 at diagnosis, acute onset, or personal and/or family history of autoimmune conditions). If Hba1c is measured more than 4 weeks before the class start date, it will be repeated at the baseline blood draw. Study laboratory tests will be reviewed by study staff to flag abnormal results, and all laboratory tests will be reviewed by study physicians (Dr. Hecht or Dr. Kim) to assess abnormalities and whether inclusion/exclusion criteria have been met. Study physicians will follow-up with participants for abnormal laboratory results that require medical follow-up. Study staff will notify participants whether they have met criteria for enrollment after screening labs have been completed.

In-person screening and consent visit: Those who successfully complete the above steps will come in for an in- person consent and screening visit. After completing written consent, they will complete additional screening and provide baseline data as follows:

- Demographics and background information
- Health history and medications to finalize screening for excluded substance abuse, mental health, medical conditions, or medications.
- Weight and height measurement and computerized tests of behavioral impulsivity and other cognitive tasks.

The above may be done remotely via Zoom if required/recommended due to COVID19. As described elsewhere in this document, other than the interaction between staff and participant being done via web-conference many aspects of this visit will be unchanged from in-person visits. Exceptions include the following: 1. Weight/height measurement will be self-reported by the participant, if possible by a photo of themselves on a home scale (provided by the study, if needed), and 2. Cognitive tasks: Our two key cognitive tasks, Delayed Discounting and Relative Reinforcing Value of Food, will be administered by staff over the internet with the participant responding from home. During in-person visits, we have been administering three additional tasks that are not primary outcomes: Food Stroop, Dot Probe, and GoNoGo. If it proves unfeasible to administer these tasks remotely (e.g. due

to the need to download specialized software and/or other limitations of the home setting), we may need to forgo these secondary tasks during periods of remote visits. If in-person visits become feasible in appropriate timeframe, we would aim to re-measure weight/height in person as well as administer any skipped cognitive tasks with participants as feasible.

All screening evaluations will be completed within 8 weeks prior to class start date.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Participants will become enrolled upon randomization, after meeting all screening criteria and completing all of the baseline assessment procedures.

Baseline Assessments

Those who complete the consent visit and whose screening labs are within range will complete the following baseline assessments from home/online: Qualtrics questionnaire (to assess baseline eating behavior, mood, stress, etc.), 24-hour diet recall, and baseline blood draw at LabCorp convenient to them. Those whose screening Craving EMA was completed more than 4 weeks before the class start date will repeat this assessment in order to get baseline data more proximal to when the intervention starts.

Blood draws and lab tests will be done at LabCorp.

Test	Rationale	Screening	Baseline	R33 Follow-up (3, 6, 9, & 12 mos)
HbA1c	Overall glucose control	x	x	x
C-peptide and GAD 65 (if indicated)	Confirms T2DM in those on insulin, screens for LADA*	x		
TSH	Rule out untreated thyroid disorder	x		
Comprehensive Metabolic Panel (including fasting glucose)	Rule out liver and kidney dysfunction; fasting glucose for follow-up HOMA-IR	x	x (for fasting glucose to compute HOMA-IR)	x
Insulin	Used to calculate HOMA-IR		x	x
hsCRP	Examine effects of the diet on cardiometabolic and inflammatory markers		x	x
NMR LipoProfile® (Without Graph)—includes lipids			x	x

*LADA = Latent autoimmune diabetes of adults; HOMA-IR = Homeostatic model assessment- insulin resistance; hsCRP = high sensitivity C-reactive protein.

COVID-19 modifications: We will make every effort to get labs for all participants at all timepoints as planned. But if it is not possible due COVID-19 or other reasons, we will use home test kits for key labs as feasible. We will use A1c measures from a physician if we cannot obtain them in these other

ways. We may also combine the screening and baseline blood draws to be obtained at the same time to reduce the number of times participants have to go to a phlebotomy site. This may be done either by adding baseline lab tests to the usual screening process lab tests, or by wating to do screening labs at the usual baseline lab draw. Combining screening and baseline labs will not alter the data we are collecting, just the logisitics for study staff and participants.

24-hour dietary recall: Despite limitations of self-report measures in assessing dietary intake, they remain an important tool to assess dietary adherence. 24-hour diet recall provides a measure that complements the ketone measure by providing overall diet composition information that cannot be obtained from ketone measures. We will use the University of Minnesota's Nutrition Data System for Research (NDSR) software to perform 24-hour diet recall (http://www.ncc.umn.edu/products/). This is a widely-used dietary analysis program that enables the collection of multiple 24-hour diet recalls and encompasses multiple foods appropriate for diets of type 2 diabetic patients. Dietary recalls will be administered by trained dietetics volunteers by co-investigator Dr. Cindy Leung, a nutrition epidemiologist with extensive history of conducting 24-hour recalls. Recalls will be entered into the NDSR software immediately after completion. Dietary recalls will be conducted without prior notification to avoid changes in diet on the reporting day. We will complete two 24-hour assessments at each study timepoint.

Craving EMA: We hypothesize that a key behavior mechanism by which training in mindfulness can improve diet adherence is through reducing eating behavior in response to food cravings. This mobile, real-time EMA approach allows us to capture eating-related behavior and that is often brief and automatic and therefore poorly suited to traditional retrospective questionnaires. Participants will complete EMA of food cravings and craving-related eating via smartphones prior to, during, and following the intervention, a total of up to 6 times, i.e. at baseline/screening, 3, 6, 9, and 12 months; baseline craving EMA will be repeated if the first/screening administration was done >4 weeks before class start date. During each of these craving-assessment periods, participants will receive mobile cravings assessment via text 3 times per day for 3 days, and a brief follow-up text the morning after each day of testing to inquire about any craving-related eating that occurred the prior night after the evening survey was completed. The text message will ask them to complete a short questionnaire regarding whether they have experienced any food-related cravings in the past few hours, whether they have eaten in response to these cravings, and what they ate. They will also be asked to rate their stress level during the day. We are aiming to have participants complete at least 8 of 12 craving EMA assessments; fewer than this constitutes a protocol deviation.

Computerized Cognitive Measures: The computer session will comprise approximately 40-45 minutes of the tasks described below. These tasks can be adjusted to be shorter than their stated length by reducing the number of trials administered. This is a common practice in neuropsychological science research. We will create a 20-30 minute battery from the following tasks:

- Delayed Discounting[36];. The DD (1 minute) assesses the extent to which individuals value delayed versus proximal rewards. Individuals who discount delayed rewards at a high rate are more likely to engage in substance abuse, overeating, or problem gambling. This 5-trial adaptation of the original Delayed Discounting,[37] task has been validated and is an effective way to assess discount rates while reducing participant burden. The primary outcome is the participant's point of indifference, which is computed with intertemporal choice tasks that present a series of discrete choices between a larger quantity of a reward

that is delayed and a smaller amount of that commodity that is available immediately. This task can be completed remotely, via internet, if an in-person visit is not feasible due to COVID-19 or other reasons.

- Go/No-Go;[38] The Go/No-Go task (~12 minutes) is a computer task that measures sustained attention and response control, also termed behavioral inhibition. Participants are asked to watch a rectangle (oriented either vertically or horizontally), and press the spacebar as quickly as possible when the rectangle's color becomes green. In contrast, when the rectangle becomes blue, participants are asked to restrain from pressing the spacebar. The primary outcome is the number of trials correctly identified, and response time, where faster performance and better capacity to inhibit responses to blue rectangles relative to green, indicates better response inhibition. This data may not be collected if in-person visits are not feasible due to COVID-19 or other reasons.
- Food Stroop.[39] The food Stroop task (~5 minutes) is an adaptation of the classic Stroop task, and thus provides an easily quantifiable measure of food preoccupation. Subjects are asked to color-name food- and weight-related words written in different-colored inks, compared with neutral words. This data may not be collected if in-person visits are not feasible due to COVID-19 or other reasons.
- Relative Reinforcing Efficacy (RRE) of Food.[40] This task (~3 minutes) measures the relative reinforcement value of tasty foods as participants indicate how much they would be willing to pay. These choices reflect decisions that people face in the real world when experiencing the motivation to eat. This task can be completed remotely, via internet, if an in-person visit is not feasible due to COVID-19 or other reasons.
- Dot Probe.[41] This modified visual probe task (~4 minutes) measures selective attentional processing of images of food relative to neutral images. The task consists of 10 practice trials and 4 blocks that each consisted of 100 experimental trials, of which 60 are target trials (food–neutral picture pairs) and 40 are filler trials (neutral–neutral picture pairs). This data may not be collected if in-person visits are not feasible due to COVID-19 or other reasons.

<u>Online questionnaires/self-report measures:</u> We will use a targeted battery of questionnaires assessing food cravings and other eating-related behaviors, as well as standard measures of psychological distress. These will be completed via Qualtrics, and can be completed at home, via the internet. Participants who prefer to come to the lab to complete these using a study computer may schedule a time to do with study staff during business hours.

- Perceived Stress Scale (PSS).[42] 10-item measure assessing the degree to which someone perceives stress.
- Patient Health Questionnaire (PHQ-8).[43] A standardized, well-validated 8-item measure of depressive symptoms.
- Reward-Based Eating Drive (RED-13).[44] The 13-item RED scale assesses three aspects of drive to eat (loss of control, lack of satiety, and preoccupation with food). Items are answered on a Likert scale from 1 (not at all like me) to 5 (very much like me). The title of the RED questionnaire provided to participants is "Eating Experiences." Example items include "I feel out of control in the presence of delicious food" and "When I start eating, I just can't seem to stop."3
- Food Craving Questionnaire - Trait Reduced Version (FCQ-T-R).[45] The 15-item FCQ-T-R assesses (1) preoccupation with food (i.e., obsessive thought about food and eating), (2)

loss of control (i.e., difficulty regulating eating behavior when exposed to food cues), (3) positive outcome expectancy (i.e., believing eating to be positively reinforcing), and (4) emotional craving (i.e., tending to crave food when experiencing negative emotion).2

- Stress-related Eating. [46] The 2 items used in the Midlife in the United States (MIDUS) study asked participants to indicate how they usually experience a stressful event using the following two items: “I eat more of my favorite foods to make myself feel better” and “I eat more than I usually do". Items are answered on a scale from 1 (a lot) to 4 (not at all). Responses are reverse-coded and summed, with higher scores indicating greater use of food in response to stress. Item correlations are good (= .80, = .81).4
- Palatable Eating Motives Scale.[47] The 19-item PEMS assesses four motives for eating tasty food (Social, Conformity, Enhancement, and Coping motives) and is modeled after the Drinking Motives Questionnaire (M. L. Cooper, 1994). Items are answered on a 5-point scale with the following options: Almost Never/Never; Some of the Time; Half of the Time; Most of the Time; Almost Always/Always. The 4-item Coping subscales captures eating as a way of coping with emotions such worry, depression or nervousness.1
- 1-item Stress Eating.[1] This 1-item measure has been shown to predict weight gain and worsened metabolic factors in times of stress. This item asks, “how much do you tend to eat when you are under moderate stress?” and is responded to on a 5-point scale from much less than usual to much more than usual.5
- Weight Efficacy Lifestyle Questionnaire – Short Form (WEL-SF).[48] The ability to adhere to a diet in the face of difficult situations, such as dietary lapses, socializing, and peer pressure is integral to long-term maintenance of intervention effect. We will assess dietary adherence self-efficacy using the 8-item scale that assesses abilities to adhere to dietary prescriptions in a variety of situations.
- Loss of control over Eating – Brief (LOCES-Brief).[49] This 7-item measure assess perceived control over one’s eating. Items are assessed on a 100mm visual analogue scale ranging from “not at all hungry” or “not at all anxious” etc., to “extremely hungry” or “extremely anxious” etc.
- Food Acceptance and Action Questionnaire (FAAQ).[50] This 10-item questionnaire applies constructs of acceptance and mindfulness to eating behavior. Higher scores indicate greater acceptance of motivations to eat. Items are answered on a 6-point Likert scale ranging from 1 (very seldom true) to 6 (always true). A summary score is calculated by summing the scores from all items – higher scores indicate greater acceptance of motivations to eat.
- Salzburg Stress Eating Scale[51]. This is a 10-item measure of stress-related eating which captures both under and overeating in the context of common stressors.
- Dutch Restrained Eating Scale.[52] This 10-item subscale of the Dutch Eating Behavior Questionnaire assesses the frequency of restrained eating behavior. Items are assessed on a 5-point likert scale ranging from 1 (never) to 5 (very often).
- Five Factor Mindfulness Questionnaire (FFMQ).[53] We will use the short-form of the FFMQ which assesses general tendencies to be mindful in experiences of daily life.
- Promis-29 (www.nihpromis.org): A collection of 4-item short forms assessing anxiety, depression, fatigue, pain interference, physical function, sleep disturbance, and ability to participate in social roles and activities as well as a single pain intensity item. The PROMIS measures a system of highly reliable, precise measures of patient–reported health status for physical, mental, and social well–being.

- Self-Compassion Scale Short Form (SCS-SF).[54] The SCS-SF is a 12-item measure that assesses dimensions of self-compassion including self-kindness, self-judgment, common humanity, isolation, mindfulness, and over-identification
- Modified Differential Emotions Scale (mDES14): This measures the frequency of positive and negative emotions during the previous week.[55]
- Body Responsiveness Questionnaire (BRQ15): This 7-item scale assesses the degree of responsiveness to bodily sensations (Daubenmier, 2005).
- Number of hours of sleep/night: We will use one item from the Pittsburg Sleep Quality Inventory (PSQI) "During the past month, how many hours of actual sleep did you get at night".[56]
- The Stanford Leisure-Time Activity Categorical Item (L-Cat): This one-item measure comprising six descriptive categories of physical activity level, ranging from inactive to very active, has been found to be reliable and sensitive to change in weight loss interventions.[57]
- Highly Sensitive Persons (HSP) scale[58]: This widely-used 11-item scale assesses an underlying phenotypic (temperament) trait characterized by deeper cognitive processing of stimuli, emotional reactivity, a greater awareness of environmental subtleties including others' affective states, and ease of overstimulation. It will be used at baseline.
- Baseline Yoga and Meditation practice: Two items to assess use of meditation and yoga over prior month (completed at baseline).
- Follow-up Diet and Mindfulness assessment: 3 items to assess use of study-prescribed vs. other diet, as well as use of mindfulness or mindful eating (completed at follow-up timepoints, 3, 6, and 12 months).
- Coronavirus pandemic impact: Brief questions to assess how the coronavirus pandemic, including shelter-in-place, affects food access, diet adherence, and emotional eating; also mindfulness practices in those in the treatment arm (completed at 3, 6, and 12 months starting in April 2020).

Weight: One of the goals of dietary adherence for persons with T2DM is weight loss. We will use the same scale to weigh participants at each time point. Height will also be measured at baseline only to allow for analyses using body mass index. If an in-person visit is not feasible due to COVID-19 or other reasons, we will ask participants to self-report weight and height. Ideally, self-reported weight will be corroborated with a photo of participant weighing on a home scale (provided by study if needed).

Randomization

Participants will be randomized to intervention groups after completion of all screening and baseline assessment steps, and before initiation of intervention. Randomization will be done approximately 2 weeks prior to the start of classes in order to minimize post-randomization drop-out due to life circumstances that might affect participant ability to attend classes (e.g. such as job loss/change, family emergency, etc.).

6.2.3 Blinding

Analysis will be performed blinded to group assignment, study physicians will be blinded as much as possible to group assignment when managing medications, laboratory testing will be performed

blinded to group assignment, and self-report questionnaires will be filled out by participants using online questionnaires that minimize potential for introducing interviewer bias. However, neither participants nor frontline study staff managing the participant enrollment and groups will be blinded to treatment arm.

6.2.4 Follow-up visits and other data collection

Follow-up assessments (3, 6 and 12 months) include the following (all described above in the baseline assessment section):

- Blood draws/laboratory tests
- Weight measurement
- Computerized tests of behavioral impulsivity and cognitive tasks
- Health history/medication changes
- Online battery of self-report questionnaires; may be completed at in-person visit if preferred (described above)
- 24-hour dietary recall
- Craving EMA

We aim to complete the follow-up visits with all participants within a 2-3 week window at each timepoint. If in-persons visits are not possible due to COVID-19 or other reasons, we will use remote procedures to collect as much follow-up data as feasible, and as described above. If in-person visits are not possible, we anticipate that only the following data elements would be affected: 1. Blood draws: may need to rely on home test kits/blood spots, thus missing some of the secondary clinical outcomes. 2. Weight measurement: based on home scale, rather than study scale. 3. Missing data for 3 cognitive tasks that are secondary outcomes and not specified in study hypotheses.

In the R33 phase, we will also get a blood draw for the laboratory tests at 9 months, along with Craving EMA and ketone monitoring.

At-Home Ketone Monitoring: Participants will be given a home ketone monitoring device (Keto-Mojo) and ketone strips, which measure beta-hydroxybutyrate. This is a glucometer device that also measures ketones from finger-stick blood if ketone strips are inserted instead of glucose strips. The device stores data, which will be checked periodically during class sessions and study visits to confirm accuracy of self-reported measurements. *Frequency*: Participants will be asked to measure ketones before dinner 3 times a week for approximately 4 weeks during the intervention (to provide more intensive self-monitoring when starting the diet) and daily over one week stretches thereafter during key study periods (3, 6, 9, and 12 months) to monitor ketosis/diet adherence. Additionally, to encourage participant self-monitoring, participants will be asked to monitor ketones 3 times per week once a month between key study periods. Participants may be asked to upload their Keto-Mojo data via Bluetooth adaptor to the Keto-Mojo smartphone app, which in turn integrates with the HeadsUpHealth app. This integration will allow participants and the study team to track ketone and blood glucose data online, rather than relying on participants to bring their meters to study classes and visits for data upload. We may also use the EMA system to send requests to check ketone levels and report values back. As needed, during study visits, participants will be asked to bring in the meter

and staff will download data on devices to provide a check on accuracy of participant reported measures.

6.2.5 Completion/Final Evaluation

The assessments to be performed at the final evaluation at are listed above (section 6.2.4).

The only potential reason for early termination that we anticipate are participant-driven, including having to move out of the Bay Area, or dislike of/unwillingness to continue to follow the study diet. We will take steps to help participants implement the study diet in a way that works well for them, in order to prevent these kinds of early terminations. Participants who experience a life event (e.g. job change, family crisis) that affects their ability to continue to attend the intervention classes will be encouraged to continue to follow the study diet and other intervention steps to the best of their ability. They will be offered course materials and handouts in order to facilitate their ability to maintain behavioral changes that they made to date. Participants who discontinue the study intervention early will be asked to remain in the study and complete follow-up assessments as originally planned. If a participant moves out of the Bay Area or otherwise is unable or unwilling to come for a study follow-up visit, study staff will work with them to complete questionnaires online and have a blood draw at a LabCorp location convenient to them.

7. SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

The key study intervention involves diet changes, which in general is a minimal risk intervention step. The risk of hypoglycemia in persons receiving medications such as insulin or sulfonylureas is a possible serious potential adverse event, however. We anticipate that with the precautions described in detail below, the risk of serious hypoglycemia will be very low. While we encountered no serious adverse events in pilot testing, there has been little careful long-term assessment of adverse events with carbohydrate restricted diets in T2DM, which means there is some uncertainty in predicting the likelihood of adverse events. Other anticipated risks include those associated with venipuncture, psychological testing, and loss of confidentiality. None of these risks are anticipated to occur at a frequency exceeding 5%.

Expected risks to the subject from the carbohydrate-restricted diet are as follows:

1. Hyperlipidemia: There have been reports this approach, which involves increases in proportion of calories from fat, causing increases in LDL cholesterol, a risk factor for heart disease. However, several clinical trials of carbohydrate restricted diets for obesity, including three of up to one-year duration, have not shown this relationship:

1. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA.* 2005;293(1):43-53.

2. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med.* 2003;348:2082- 2090.

3. Stern L, Iqbal N, Seshadri P, et al. The effects of low- carbohydrate versus conventional

weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med.* 2004;140(10):778-785.

We will monitor serum fasting lipid profiles at baseline, 3, 6, 9 and 12 months to assess this potential risk.

2. Hypoglycemia: The carbohydrate restricted diet may lead to decreases in glucose levels. In persons receiving medications such as sulfonylureas or insulin, this could increase the risk of hypoglycemia if appropriate medication adjustments are not made. Study physicians will oversee changes in medications, specifically reductions (or discontinuations if at a low dose) in an order that typically prioritizes reductions/discontinuations as follows: (1) insulin, (2) sulfonylureas, (3) megltinides (secretagogues), (4) SGLT-2 inhibitors, (5) GLP-1 agonists and DPP4 inhibitors, (5) thiazolidinediones (TZD). Biguanides (e.g., metformin) are typically continued unless glycated hemoglobin levels (HbA_{1C}) are consistently below 6.5%. Initial medication adjustments typically involve reducing a medication dose by half, and are aimed at preventing hypoglycemia when initiating carbohydrate restriction. The number of medications reduced is calibrated based on initial HbA_{1C} levels, with limited medication reductions in participants with high HbA1c levels and more extensive reductions in persons with HbA_{1C} levels in the low diabetic range. For example, a participant with a HbA_{1C} level greater than 8.0% might have a recommendation to reduce insulin doses in half while continuing other medications, while a participant with a HbA_{1C} level between 6.5% and 7.0% might have a recommendation to stop using all diabetes medications other than biguanides and thiazolidinediones. The table below has some typical medication reductions; these reductions are examples that need to be individualized based on the combination of medications the participant is using.

Initial HbA1c	Typical initial medication reduction
6.5-7.0%	• Continue: Metformin, TZD • Reduce by 50%: GLP-1 ag/DPP4 inhibitor • Stop: Secretagogue, insulin, acarbose, SGLT-2 inhibitors
7.1-8.0%	• Continue: Metformin, TZD, GLP-1 ag/DPP4 inhibitor • Reduce by 50%: long-acting insulin, secretagogue, SGLT-2 inhibitors • Stop: Acarbose, short- and intermediate-acting insulin
8.1-12%	• Continue Metformin, TZD, secretagogue, basal insulin, GLP-1 ag/DPP4 inhibitor • Reduce by 50%: intermediate and long-acting insulin, • Stop: Acarbose, short-acting insulin

TZD: thiazolindinedione; secretagogue: sulfonylureas and megltinides; GLP-1 ag: glucagon like peptide 1 agonist; DPP-4 inhibitor: dipeptidyl peptidase 4

For the first 6 weeks of the trial, participants will receive recommendations for fingerstick blood glucose (FBG) monitoring while adapting to the reduced carbohydrate diet, which will be tailored by study physicians to their diabetes medication regimen. The FBG measures are for safety monitoring and guidance of medication adjustment, and are not used for data analyses. Participants on non-insulin medications with a risk of hypoglycemia (e.g. secretagogues) will typically be asked to check FBG fasting and pre-dinner. If taking insulin, participants will typically be asked to check FBG before each injection (standard of care), in addition to a fasting FBG. Participants taking only metformin will

typically not be asked to monitor FBGs. FBGs will be reviewed on a weekly basis by study physicians. If the majority of FBG values drop below 110, or there are other concerning FBG patterns, we will typically reduce/stop medications in the order noted above.

Study physicians will review these medication adjustments as well as any symptoms reported by participants using information collected from participants on a weekly basis during the initial 12 week intervention period, and will communicate suggested changes in diabetes medications to participants. Study participants will be able to contact study staff using a study phone number for questions or problems, and staff will be able to reach study physicians by pager or cell phone for more urgent problems. As in our pilot study, primary care physicians for participant will receive information about the study before the participant begins the study. Study physicians will help to make sure that primary care physicians informed of any suggested changes to medication regimens, and will consult with primary care physicians where indicated.

3. *Other theoretical risks* of the carbohydrate restricted diet include nephrolithiasis and increased bone turnover. The potential for these side effects is derived from pathophysiologic theory, studies of the diet using intermediate endpoints, and extrapolation from similar diet approaches, such as the ketogenic diet for epilepsy. Because kidney stones and bone fractures have not been reported as an actual adverse effect of this diet in the adult research literature, we cannot estimate their frequency. We will be recording adverse events that occur during the study.

4. *Minor adverse effects*: With this diet, several minor side effects may occur and include constipation, headache, muscle cramps, diarrhea, general weakness, and rash. Most of these occur at diet initiation, are short-lived, and are generally alleviated by adequate fluid intake and other minor diet modifications that will be thoroughly addressed in the intervention. Participants will be instructed to speak to the instructor *or contact study staff* if they experience discomfort, such as constipation, diarrhea, weakness, muscle cramps, or dizziness. There is extensive instruction during class on how to address any potential side effects stemming from the diet.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Unanticipated problems will be recorded in the study database throughout the study. We will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. During the initial 11 to 12 week intervention period, participants will receive a weekly survey that will include questions about AE/SAEs. At each subsequent study visit, participants will be asked about the occurrence of AE/SAEs since the last visit. We will monitor serum fasting lipid profiles at baseline, 3, 6, 9 and 12 months. Events will be followed for outcome information until resolution or stabilization.

Safety parameters will be reviewed and analyzed per the schedule below.

Data type	Frequency of review	Reviewer
AEs and rates (including out-of-range lab values)	Monthly	PI, Internal QA Reviewer
	Twice annually	Independent Monitors
	Annually	NCCIH

SAEs (unexpected and related)	Per occurrence	PI, Independent Monitors, NIH/NCCIH
SAEs (expected or unrelated)	Per Occurrence	PI, Internal QA Reviewer
	Twice annually	Independent Monitors, NIH/NCCIH
Unanticipated Problems	Monthly	PI, Internal QA Reviewer
	Per Policy	IRB

Study progress and safety will be reviewed monthly (and more frequently if needed). Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the Monitoring Committee semi-annually. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitor and will be forwarded to the IRB and NCCIH. The IRB and other applicable recipients will review progress of this study on an annual basis

7.3 Adverse Events and Serious Adverse Events

An **adverse event (AE)** is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recording regardless of their relationship to the study intervention.

A **serious adverse event (SAE)** is generally defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

Laboratory values that will be collected to assess safety: We will monitor serum fasting lipid profiles at baseline, 3, 6, 9 and 12 months. Abnormal lipid values are defined using the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 criteria provided below (https://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.02_2009-09-15_QuickReference_5x7_Locked.pdf).

Adverse Event: Hypertriglyceridemia
Short Name: Hypertriglyceridemia
MedDRA Code: 10020870

Grade	Description
1	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L
2	>300 mg/dL - 500 mg/dL; >3.42 mmol/L- 5.7 mmol/L
3	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L
4	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences

5	Death

Adverse Event: Cholesterol high

Short Name: Cholesterol high

MedDRA Code: 10008661

Grade	Description
1	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L
2	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L
3	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L
4	>500 mg/dL; >12.92 mmol/L

AEs to be collected as solicited events at study visits include recent hospitalizations and hypoglycemic episodes. Unsolicited events will be recorded in the study Salesforce database. AE data that is formally assessed at study visits will be compared to existing unsolicited events in participant records to avoid double capture.

7.4 Reporting Procedures

Serious Adverse Event reporting will be in accordance with the UCSF IRB Regulations (http://irb.ucsf.edu/sites/hrpp.ucsf.edu/files/post-approval-reporting-summary-sheet.pdf) and Code of Federal Regulation Title 21 Volume 5 Part 312.32.

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- A detailed description of the adverse event, incident, experience, or outcome;
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

Adverse Event Reporting

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Safety Monitor(s), UCSF IRB, and NCCIH in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer, and Independent Safety Monitor(s) within 3 days of the investigator

becoming aware of the event. Other serious and unexpected AEs related to the intervention will be reported within 5 working days.

- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Safety Monitor(s), IRB, and other oversight organizations in accordance with their requirements and will be reported to NCCIH on an annual basis.
- All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the Independent Monitors. The Independent Safety Monitor(s) Report will state that all AEs have been reviewed.

7.5 Follow-up for Adverse Events

Adverse Events will be followed for outcome information. Study personnel will follow-up with participants on a regular basis (frequency to be determined by the nature of the problem) until the problem has resolved or stabilized. These contacts may be made by the PI or other study physician or personnel (including staff, Project Director) and will be done via phone and/or email or text as the PI deems appropriate depending on the event and situation, and taking into account participant preference as reasonable.

7.6 Safety Monitoring

While the overall risks of this study are low, due to clinical trial design and the use of a treatment that has a low but possible risk of serious adverse effects, we will employ a three-person data safety-monitoring board with outside reviewers. The outside reviewers will not otherwise be part of the study team, and will include an experienced clinical investigators and statistician. The reviewer's CVs will be submitted to NIH, and agreement will be obtained from NIH that the reviewers are suitably qualified before beginning the study. The PI will ensure continuous and close monitoring of participant safety. The PI will report to the DSMB. Study progress and safety will be reviewed weekly by the PI and core study team. A report that will be submitted to the outside reviewer will be compiled twice a year and will include a list and summarization of adverse events. In addition, the report will address (1) whether adverse event rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; and (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study. If the DSMB requires an interim analysis based on the occurrence of severe adverse events, we will develop plans for conducting these in consultation with the statistician on this RCT. The outside monitoring reports will be increased in frequency if two or more Serious Adverse Event's (SAE's) with attribution to study related procedures as possibly, probably or definitely related occur in a six-month period of time. In this situation, SAE's will be reported monthly, and study procedures will be reviewed to determine if changes are needed to reduce the risk of SAEs.

Steps Emanating from Data Review: The DSMB will be able to recommend amendments to the protocol, changes in study procedures, changes to the data collection plan or study forms, or study termination due to safety or other issues. Should recommendations be made to amend the study protocol or terminate the study, these recommendations and planned responses will be forwarded to the NIH program officer within 10 working days. Should the protocol be amended as a result of data review, the UCSF IRB will be notified and the amendment approved prior to study amendment implementation unless the protocol amendment must be implemented to protect the immediate

safety of the study subjects. In such a case, the protocol amendment will be immediately implemented and the UCSF IRB will be notified directly after protocol amendment implementation.

The PI will be the primary individual responsible for data and safety monitoring. The DSMB Chair will not be named as a co-investigator on this RCT and will serve as a secondary safety monitor determine what steps should be taken to manage AEs and SAEs if/when they occur. In the event that a SAE is identified, the DSMB Chair will schedule a full meeting of the DSMB and review the results of the SAE report from the UCSF CHR prior to this meeting. The decisions of the IRM and the DSMB will assist Dr. Hecht with developing plans to implement this RCT in a manner that minimizes research-related risks to participants.

DSMB Reviews. Twice yearly DSMB meetings will be held via teleconference. Where a SAE occurs, a special closed meeting of the DSMB will be convened to determine what changes if any are necessary and if the RCT should be stopped.

8. INTERVENTION DISCONTINUATION

Stopping Guidelines: No interim analyses are planned and we do not anticipate stopping the study early. The primary clinical outcome variable, HbA1c, is a surrogate marker for long-term risk of clinical events in diabetes, but is not an outcome that would justify early termination rules for a study of this size and duration. However, the occurrence of any serious adverse events related to intervention or assessment procedures will be reviewed at length by the DSMB in separately scheduled, closed meetings (if or when severe adverse events occur) to determine whether the study should be stopped. Where the DSMB considers issues related to participant safety, the DSMB Chair will moderate closed sessions and take a formal vote from DSMB members as to whether the trial should continue given the occurrence of the adverse event(s).

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Our **primary objective** is to test the hypothesis in this study is that **mindfulness training will improve adherence to a carbohydrate restricted diet in type 2 diabetes**. We will test this hypothesis using a randomized, controlled trial design comparing nutrition education alone (Ed arm) to nutrition education plus training in mindful-based intervention components including mindful eating practices (Ed +MBI). Our primary adherence measure is the proportion of ketone measures $\geq$ 0.5 mmol/L. An additional adherence outcome measure will be the proportion of participants consuming 50 g/day or less of non-fiber carbohydrate, using 24-hour diet recall.

A **second aim is to test several hypothesized pathways by which the MBI components will influence dietary adherence**. We aim to test evidence that these pathways are associated with improved adherence, increased by the mindfulness intervention, and play a role in mediating intervention effects on adherence. These pathways and their associated measures are as follows:

- Mindfulness training will reduce **frequency of eating in response to cravings** as a result of enhanced ability to address food cravings. This is our most important mechanistic pathway.

Our key measure of this mechanism is frequency of eating in response to cravings using ecological momentary assessment (EMA).

- Enhanced ability to reduce craving-related eating/**decreased impulsivity** as measured by the Relative Reinforcing Value of Food or Delayed Discounting task.
- **Decreased emotion-related eating** as measured by the Coping subscale of the Palatable Eating Motives Scale (PEMS).
- **Decreased stress- related eating** as measured by two questions about stress-related eating from the MIDUS study. We will also look at an additional item about stress- eating.[1]
- **Improved resilience** (resumption of dietary adherence) after dietary non-adherence occurs. Our key measure will be the time from a ketone measure of < 0.5 mmol/L to higher levels of ≥ 0.5 mmol/L, indicating a return to nutritional ketosis after a period of consuming foods that depress ketosis.

A **third aim is to test optimal maintenance strategies**, using an adaptive intervention trial design during the maintenance phase (described further in sections on the maintenance phase). We will compare low to medium intensity maintenance programs for persons with good adherence in the intervention phase (above the median ketone values), and compare medium and high intensity maintenance strategies in persons with weak adherence in the intervention phase (below the median ketone values). Outcome measures during maintenance will the same as described for comparisons between Ed and ED = MBI groups (i.e. ketones ≥ 0.5 mmol/L will be the primary outcome measure, and we will also assess secondary adherence outcomes).

A **fourth aim will be to compare clinical outcomes** (e.g. HbA1c, weight, HOMA) between intervention arms.

9.2 Sample Size and Randomization

Target sample size: n=120 for enrollment in the second/R33 phase. We assume 10% loss to follow-up, with a target sample size for analysis of n=108. Many analyses in the R33 phase will use only R33 data, but a few analyses, specified below, will use data combined from the R61 (with n=58 participants) and R33 phases of this project. Combined analyses will only use data out to the 6 month timepoint, the end of the R61 phase follow-up.

Our primary outcome in the R33 phase will be adherence to carbohydrate restriction, defined as proportion of ketone measures ≥ 0.5 mmol/L. For sample size calculations, we treat the % of blood samples with ketones of ≥ 0.5 mmol/L as a continuous variable, and compare arms across intervention groups. Based on our prior data, we estimate that about 45% of the samples in the Ed arm will be ≥ 0.5 mmol/L (SD 37 %). We assume that after drop out of 10% (a conservative estimate as we had < 5% dropout in the R61 phase), we will have about 54 persons (of the original n=60) in each intervention group for evaluation of adherence to carbohydrate restriction. We will be able to detect a statistically significant difference in adherence (using percent of ketone measures ≥ 0.5 mmol/L) with 80% power (alpha=.05) between intervention groups if the difference in adherence between arms is 20 percentage points or greater (e.g. 45% versus 65%).

In the R33 phase, an important aim is to test whether our hypothesized mechanisms (e.g., craving related eating) are correlated with diet adherence measures (% of blood samples positive for ketones). Based on the simplifying assumptions of linear regression with one observation per person

that summarizes craving-related eating and diet adherence measurements in the week following the intervention, and using our overall sample of N=120 and assuming 10% dropout (N = 108), we will have 80% power to detect a statistically significant correlation if the true correlation coefficient (*r)* is .267 or greater. If we look just at the Ed+MBI group (N = 54), we will have 80% power to detect a significant correlation if the true correlation coefficient (*r)* is .375 or greater. In addition, for this outcome, we plan to combine data across the closely linked R61 and R33 phases of this project to increase our statistical power. Using our anticipated overall sample of N=164 (accounting for dropout), we will have 80% power to detect a statistically significant correlation if the true correlation coefficient (*r)* is 0.217 or greater. Correlations below these levels will suggest that our hypothesized mechanisms are not strongly linked to diet adherence. We anticipate equal or greater power in our repeated measures analysis depending on the within-person correlation of our outcome measure.

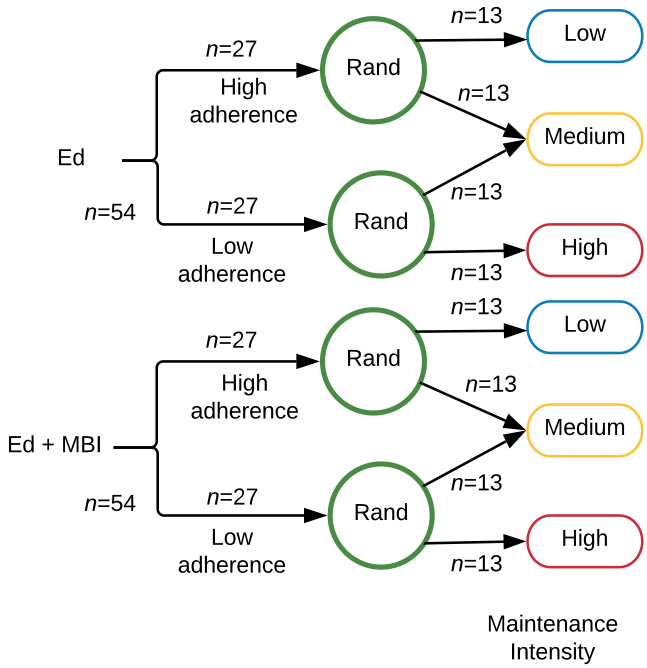


Figure 2: Intervention and maintenance groups. We aim to enroll 120 people; n's account for 10% attrition. Maintenance groups will be conducted separately by intervention arm (Ed or Ed+MBI) but for some analyses, similar intensity groups (e.g. low) will be combined

We will also compare adherence between the different adaptive intervention maintenance arms. We will allow for a 10% dropout after the main intervention period (in SUCCEED it was 3% at this stage), leaving 108 participants to be assigned to maintenance strategies. Participants will be randomly assigned to maintenance intensity based on diet adherence, using ketone at the end of the intervention phase. We consider ketone levels of $\geq$ 0.5 mmol/L to be evidence of target carbohydrate restriction. Those with *above* the median proportion of ketones measures $\geq$ 0.5 mmol/L within their intervention group will be randomized (1:1) to the Low or Medium intensity maintenance arm. Those with *below* the median proportion of ketones measures $\geq$ 0.5 mmol/L within their group will be randomized (1:1) to the Medium or High intensity maintenance arm (any persons exactly at the median will be randomly assigned to one of the three maintenance intensities). Thus for each adherence group (above or below the median) we have about 27 people in each maintenance intensity (low versus medium intensity for the above the median adherence group, and medium versus high intensity for the below the median adherence group), with half the participants in each maintenance group originating from each of the two intervention arms (about 13 persons in each

maintenance group). As noted, we will consider a p-value of < .1 to be evidence that one maintenance arm may be superior for application in future trials. For sample size calculations, we treat the % of blood samples with ketones of $\geq$ 0.5 mmol/L as a continuous variable, and compare maintenance arms across intervention groups but within the groups defined before maintenance as above vs. below median % of days in ketosis , using a *t*-test, and we will then do the same comparison stratified on the intervention arm. Based on our data, we estimate that about 75% of the samples in the "above median ketones" arm will be $\geq$ 0.5 mmol/L (SD 12%). We will be able to detect a statistically significant difference in adherence (using percent of ketone measures $\geq$ 0.5 mmol/L) with 80% power (alpha=.1), in the above the median adherence groups (using participants from both the Ed and Ed+MBI arms) if the true difference in percent adherence between adaptive maintenance arms (low. vs. medium) is 8.2 or greater (e.g. 75% versus 83.2%). We will also perform stratified analyses within the Ed and the Ed+MBI arms, and will have 80% power to detect a 12% points or greater difference in adherence between adaptive maintenance arms in.

Treatment Assignment Procedures

Participants will be randomized in a 1:1 fashion to one of two study groups (Ed or Ed+MBI), using block sizes of 4-6, and stratifying by BMI (above and below BMI of 25). We do not have a sample size goal for each stratum, but we want to ensure that the two arms have approximately equal numbers of normal weight participants.

Randomization to intervention group and maintenance phase track will be done via the Salesforce database. The randomization table will be programmed by a database manager, who is not otherwise involved in any enrollment or other participant procedures. Randomization will be done via the Project Director, Dr. Moran, who will not have access to the randomization table. When a participant ID number is entered into the database by study staff, a group assignment is revealed. This provides a computerized group assignment that cannot be altered by study staff and the group assigned is immediately recorded in the study database.

9.3 Definition of Populations

Intent to treat (ITT): Intent to treat is defined as the population that has been randomized, regardless of class attendance.

Per protocol: Per protocol is defined as the population that has been randomized and attended who attend at least 2/3 of weekly group sessions.

9.4 Interim Analyses and Stopping Rules

No interim analyses will be performed and we do not anticipate stopping the RCT early. The primary clinical outcome variable, HbA1c, is a surrogate marker for long-term risk of clinical events in diabetes, but is not an outcome that would justify early termination rules for a study of this size and duration. However, the occurrence of any serious adverse events related to intervention or assessment procedures will be reviewed at length by the DSMB in separately scheduled, closed meetings (if or when severe adverse events occur) to determine whether the RCT should be stopped or enrollment suspended. Where the DSMB considers issues related to participant safety, the DSMB Chair will moderate closed sessions and take a formal vote from DSMB members as to whether the trial should continue given the occurrence of the adverse event(s).

9.5 Outcomes

9.5.1 Primary Outcome

Primary behavioral adherence outcome: For the R33 phase, the primary outcome will be to compare diet adherence between intervention arms. Our key adherence measure is proportion of ketone measures dichotomized as $\geq$ 0.5 mmol/L versus <0.5. We will use Student's t test to compare the proportions of ketone measurements at each assessment time (3, 6, 9, and 12 months) that are $\geq$0.5 mmol/L between study groups as an initial analysis step, but mixed effects models assessing group differences over time will be our primary analysis approach. Analysis approaches are discussed further in section 9.6 on data analysis.

9.5.2 Secondary Outcomes

Secondary adherence outcomes: We will also compare proportion of participants consuming < 50 grams/day of non-fiber carbohydrate, and mean grams of non-fiber carbohydrate consumed per day (from 24-hour diet recall) between groups, initially using Pearson's Chi square test and then using a mixed effects logistic regression of the dichotomized carbohydrate measure to get estimates of between-group differences at the end of the initial intervention (3 months) and at the end of the adaptive maintenance follow up (12 months). As an additional diet adherence metric, we will also compare non-fiber carbohydrate consumption per day between groups, using a log transformed value as a continuous variable.

Mechanistic outcome(s): Our primary hypothesized mechanism is reduction in **frequency of eating in response to cravings** as a result of enhanced ability to address food cravings with mindfulness training. Our key measure of this mechanism is frequency of eating in response to cravings using ecological momentary assessment (EMA). In the R33 phase this outcome will be measured at baseline, 3, 6, 9, and 12 months.

Additional mechanistic outcomes: We have four additional mechanistic measures to assess our hypothesis that mindfulness training will enhance dietary adherence:

- Strengthened executive functioning /decreased impulsivity as measured by the Delayed Discounting task. As the importance of impulsivity may be modified by the responsiveness to food cues, we will also measure this with the Relative Reinforcing Value of Food (RRVF) and look at this as an effect modifier.
- Decreased emotion-related eating as measured by the Coping subscale of the Palatable Eating Motives Scale (PEMS).
- Decreased stress-related eating as measured by the 2 questions about stress-related eating from the MIDUS study. We will also look at an additional item about stress- eating.[1] We will also measure overall perceived stress using the PSS.
- Improved resilience (resumption of dietary adherence) after dietary non-adherence occurs. Our key measure will be the time from a ketone measure of < 0.5 mmol/L to higher levels of $\geq$ 0.5 mmol/L, indicating a return to nutritional ketosis after a period of consuming foods that depress ketosis.

Clinical outcomes:

- Glycemic control, using HbA1c. We view improving HbA1c as the primary clinical outcome that we seek to improve in subsequent studies.
- Fasting glucose
- Homeostatic model assessment (HOMA) index of insulin resistance (computed from insulin and fasting glucose measures)
- Weight

9.6 Data Analyses

Overall analysis approach: Preliminary analysis will be performed to confirm that key data variables are clean and complete in prepared datasets. Baseline patient characteristics will be compared between intervention groups to assess whether important characteristics were evenly distributed during randomization. General analytic approaches will include estimation of odds ratios and risk differences plus chi-square tests for categorical variables compared across groups, rates of change with confidence intervals plus McNemar's test for categorical variables compared pre/post-intervention within groups, and t-tests and multiple linear regression for comparing continuous variables between groups.

The principal analysis will use intent-to-treat methods in which all observations will be included for individuals based on initial group assignment, regardless of adherence to the treatment protocol. As a secondary analytic method, we will also perform as-treated analyses with those who attend at least 2/3 of weekly group sessions. We recognize the challenge of missing data in assessing clinical trial outcomes. We will take extensive steps to limit missing data. Our team has extensive experience in study retention; in our SUCCEED T2DM study, outcome assessment was completed in 97% of participants at 12 weeks. For our primary mechanism measure, eating in response to cravings using EMA, data can be obtained even for persons who move or have to travel. Finally, we will employ mixed-effects models and maximum likelihood estimation to address missing data.

Addressing COVID-19 related protocol changes: As noted, we have had to make changes in the delivery of the intervention content from in-person to video conferencing (Zoom) due to the COVID-19 epidemic. While we have taken steps to minimize the intervention differences in this change, we cannot eliminate all differences. To examine and account for the potential effects of the change in delivery mode on our outcomes, we will include a variable indicating whether video conferencing was used in intervention delivery at some point for the participant during the main intervention period in the first 3 months (yes/no) to adjust for delivery mode in outcome analyses. We will include a similar variable in analyses of outcomes that include the maintenance period (any video conference delivery, yes/no). Secondly, we will compare outcomes within intervention arms between waves with and without use of video conference delivery. This will be used to test whether outcomes appear to be comparable between in-person and video conference delivery. We will also add some brief questions to the battery of self-report measures that are collected at 3, 6, and 12 months to assess how the coronavirus pandemic, including shelter-in-place, affects food access, diet adherence and emotional eating triggers.

9.6.1 Analysis of Primary Outcomes

To assess dietary adherence (ketone levels), we will first dichotomize ketone data as "ketosis" (values $\geq$ 0.5 BOHB mmol/L in fingerstick blood) and "not ketosis" (values < 0.5 BOHB mmol/L in fingerstick

blood). We have dichotomized ketone levels based on our use of this level as an indicator that participants are engaging in adequate CR to achieve nutritional ketosis. Next, we will analyze these dichotomous ketone outcome in a mixed effects logistic regression model with random effects for study period nested within person, as each participant provides ketone data over seven days for one week within each study assessment period (3, 6, 9, and 12 months). We will include (as fixed effects) study period, randomization group, and their interaction term. We will estimate differences between randomization groups at each time point and differences between time points within each randomization group. We will employ similar approaches for analyzing the dichotomous outcome of consuming $\leq$ 50 g/day nonfiber carbohydrate per day, versus > 50 g/day. This outcome will be dichotomized based on the mean of two measures at each of three timepoints. We will also explore models treating ketone and non-fiber carbohydrate consumption data continuously using the similar model specifications as described above in a mixed-effects model. This will yield average differences in the ketone levels and quantity of non-fiber carbohydrate consumption between randomization groups and within time points.

9.6.2 Analysis of Secondary Outcomes

Our main secondary mechanistic and clinical outcomes are continuous measures. To assess changes each of these measures across groups and over time we will use ANCOVA and linear mixed methods. In mixed models, we will include a random person effect, as well as fixed effects including study period, randomization group, and their interaction term. We will estimate differences between randomization groups at each time point and differences between baseline and subsequent time points within each randomization group.

The primary analysis approach for assessing whether each behavioral mechanism is associated with dietary adherence will use regression analysis, and use dietary adherence as the model outcome and the proposed mechanism including craving-related eating as predictor. We will treat as a continuous outcomes (1) the proportion of blood ketone measures $\geq$ 0.5 mmol/L in a given study period (primary outcome), and (2) number of grams of non-fiber carbohydrate consumed per day (taking the mean of two measures per time point using 24-hour diet recall). We will also look at carbohydrate intake dichotomized based on the continuous measure of the 24-hour diet recall defined as consumption of $\leq$ 50 g/day of non-fiber carbohydrate vs. >50g/day. Craving-related eating will be defined as the proportion of responses in each study period when a participant reported eating in response to craving. We will use combined data from the R61 and R33 phases for outcomes to 6 months, as well conducting analyses for each phase alone, which includes outcomes at 9 and 12 months for the R33 phase.

Comparison of maintenance strategies. We will compare adherence measures across the randomized arms in maintenance phase. As the intention here is to inform the design of a subsequent efficacy trial, we will consider a p-value of < .1 to constitute potential evidence of an advantage of a maintenance arm. If we do not find evidence of benefit of a more intensive initial maintenance strategy, the less intensive arm will be considered the preferred arm for a future trial.

9.7 Blinding of study analysis. To blind the study statistician and investigative team, the intervention arms will be labeled arms “A” and “B”, and the study statistician and key study investigators will not know the identity of the arms until after initial data analysis has been performed.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Data will be collected by trained research assistants and study coordinators, using paper forms, as well as via online questionnaires using *Qualtrics.* All surveys and forms will be de-identified and coded with a unique subject number that will not contain personally identifiable information, such as subject initials or birthdates. During the COVID-19 epidemic, we will replace paper forms with online data collection forms where appropriate to facilitate remote enrollment and entry of data.

10.2 Data Management

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports will be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete.

This study will use a Salesforce database. The database will be secured with password protection. The statistician will receive only coded information that is entered into the database under those identification numbers. Electronic communication with outside collaborators will involve only unidentifiable information. The database incorporates an electronic audit trail to show change(s) to data after original entry including the date/time and user making the change. Paper data collection forms will be used to collect a limited amount of data (e.g. health history and medications, weight), which will be entered into the Salesforce database after undergoing systematic review for completeness, accuracy, and adherence to study protocols.

10.3 Quality Assurance

10.3.1 Training

All study staff will complete CITI human subjects training. This will be tracked and reviewed by the Project Director yearly or more frequently, with submission of each IRB modification or renewal (i.e. at least yearly). Study staff will also receive training from Dr. Moran on all study screening, enrollment, and assessment procedures, including data collection review and entry procedures. Trainings will incorporate both didactics as well as observation and modeling of appropriate procedures and conduct.

10.3.3 Metrics

Much of our data will be electronically and automatically captured (e.g. lab results), but we plan several steps to ensure data quality. EMA data will be reviewed on a weekly basis and questionable responses will be clarified with participants. For Qualtrics questionnaires, we will utilize range checks and other automated steps to prevent or check unusual responses; programing will be performed to require responses to key data elements. Lab results will be reviewed for clinical reasons before providing to participants, and unexpected values will be followed-up to ensure accuracy. The accuracy of hand-entered data will be checked via automatic checks for out-of-range values.

QA review and data verification will be performed by someone other than the individual originally collecting the data, or by double-data entry. The database will include programing to prevent or identify out of range values. We will use our study database to plan upcoming follow-up visits and ensure that these are appropriately scheduled. The database will also be used to identify any visits that are at risk of being overdue so that follow-up steps can be taken. A statement reflecting the results of the ongoing data review will be incorporated into the Annual Report for the Independent Safety Monitor(s).

10.3.4 Protocol Deviations

Protocol deviations will be captured by regular review of cases during the enrollment process by Dr. Moran to ensure that eligibility criteria are met. Key points of review include post-consent visit and baseline lab completion as well as before randomization. Checks will also be programmed into Salesforce to ensure that enrollees have completed necessary steps to enrollment. Deviations in data collection procedures will be captured via the following standard procedure: after each participant visit, the study staff member who conducted the visit will review the folder and data collection forms. A second review will be done by another staff member who wasn't involved in the data collection before data entry. Any discrepancies or potential problems will be documented and reviewed with Dr. Moran (or, over time and with training and supervision, with one of the lead study coordinators). Dr. Moran will periodically spot-check random participant folders to ensure compliance with procedures.

10.3.5 Monitoring

Protocol compliance and monitoring will be done via review of records and forms after each participant visit before data entry. Review will be done by a study staff member who was not involved in the data collection for that participant, and any discrepancies or potential problems will be reviewed by the Dr. Moran (Project Director). Dr. Moran will periodically spot-check random data collection forms to ensure compliance with procedures.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

The protocol and the informed consent documents (Appendix A) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study.

11.2 Informed Consent Forms

Signed consent forms will be obtained from each participant, using IRB-approved consent forms and procedures. The consent forms will describe the purpose of the study, the procedures to be followed, and the risk and benefits of participation. A copy will be offered to each participant and this fact will be documented in the participant record. If in-person visits are not possible due to COVID-19 or other reasons, consent to participate in the full-study will be completed via Docusign, for which the UCSF IRB has provided blanket approval during COVID-19.

11.3 Participant Confidentiality

Participants will be assigned unique, coded, confidential identifiers (code numbers), which will be used to label all data forms, data entries and biological specimens, including LabCorp lab slips and

results. Identifiable information, such as name, will not appear on these materials. The key linking the subject's identity to their unique coded identifier will be kept in a confidential manner in a database on a secure UCSF server, with access only by the principal investigator and the research staff. No names or individual identities will be used in publications resulting from the study. Physical records will be kept in an area accessible only to research staff. Research data will be stored on a secure, HIPAA-compliant server and drive with monitored and controlled access for study staff and investigators. The web-based survey will be hosted on secure servers. In addition, participants will enter only a study ID number, thus no identifying information will be associated with their questionnaire data. Online data collection avoids or minimizes the transfer of personally identifiable information, and uses industry best practices for protection of data. On the ERN forums, users are identified by self-selected screen names. Other users cannot see their email address or other identifying information. Participants must use an email address to register to use the ERN, Keto-Mojo, and HeadsUpHealth apps. Participants will told that if they choose, they can use an anonymous email address that is not connected to their identity for this process, and staff will offer to assist them in acquiring such an address if they wish. If they choose to do this, then the risk of privacy loss resulting from a breach in security from these companies is reduced. The web-conferencing platform, Zoom, that we are using to conduct study classes and study visits remotely due to COVID-19, is HIPAA compliant. At UCSF it is already in use for remote medical visits, with necessary business associate agreement and procedures in place to ensure HIPAA-compliance.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

13. PUBLICATION OF RESEARCH FINDINGS

Conference abstracts and manuscript will be made available for review by study co-investigators included on the publication prior to submission.

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15. SUPPLEMENTS/APPENDICES

Appendix A:

i. Consent form (Main Study)

ii. Consent for Screening Tests