PennState

HRP-591 - Protocol for
Human Subject Research

Protocol Title:
Decreasing Stress in Diabetes: A Randomized Controlled Trial (DE-STRESS)

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1.0 Objectives

1.1 Study Objectives

The purpose of this study is to conduct a randomized controlled trial to determine the effects of a 6-month live online Mindfulness-based stress reduction (MBSR) intervention compared to an active control Stress Management Education (SME) on glucose control in adults with uncontrolled diabetes. We will randomize 290 adults with uncontrolled diabetes to a 6-month MBSR intervention or SME control. Both MBSR and SME will be delivered online by experienced instructors in a live interactive virtual classroom using videoconferencing. Outcomes will be assessed at baseline, a follow-up phone call after Class #4, and study visits at 2-months and 6-months. The specific aims of the study are:

Specific Aim 1: To conduct a randomized controlled trial to determine the effects of a 6-month live online MBSR intervention compared to an active control SME on glucose levels in 290 adults with uncontrolled diabetes. The primary outcome will be hemoglobin A1c (HbA1c), a measure of the average glucose level over the past 3 months. *We hypothesize that between the two groups, there will be a clinically significant 0.5% absolute difference in the mean change in HbA1c from baseline to 6-months.* We will also look at the 2-month HbA1c, however it may be too brief a time period to fully capture the impact of MBSR. An absolute reduction in HbA1c of 0.5% would be expected to reduce the risk of any diabetes-related complication by at least 10% (Stratton et al., 2000). We will assess fasting glucose as a secondary outcome as it is linked with adverse health outcomes (Barr et al., 2007; Schmidt et al., 2005), and can be lowered with MBSR based on our pilot study (Raja-Khan et al., 2017).

Specific Aim 2: To determine the effects of live online MBSR compared to SME control on psychosocial, behavioral and physiological mechanisms potentially mediating the effects of MBSR and/or SME on glucose levels in adults with uncontrolled diabetes. Secondary outcomes include: diabetes-related distress, subjective stress, craving, the impact of COVID-19 on subjects' lives, and subject expectancy. Adverse Childhood Experiences (ACEs) will be assessed at baseline. *It is hypothesized that these measures may mediate the effects of MBSR and/or SME on glucose.*

1.2 Primary Study Endpoints

The primary outcome will be hemoglobin A1c (HbA1c) at the 6-month visit, a measure of average glucose control over the past 3 months.

1.3 Secondary Study Endpoints

Secondary outcomes include: diabetes-related distress, subjective stress, craving, the impact of COVID-19 on subjects' lives, subject expectancy, and other physiologic, behavioral and psychosocial measures.

2.0 Background

2.1 Scientific Background and Gaps

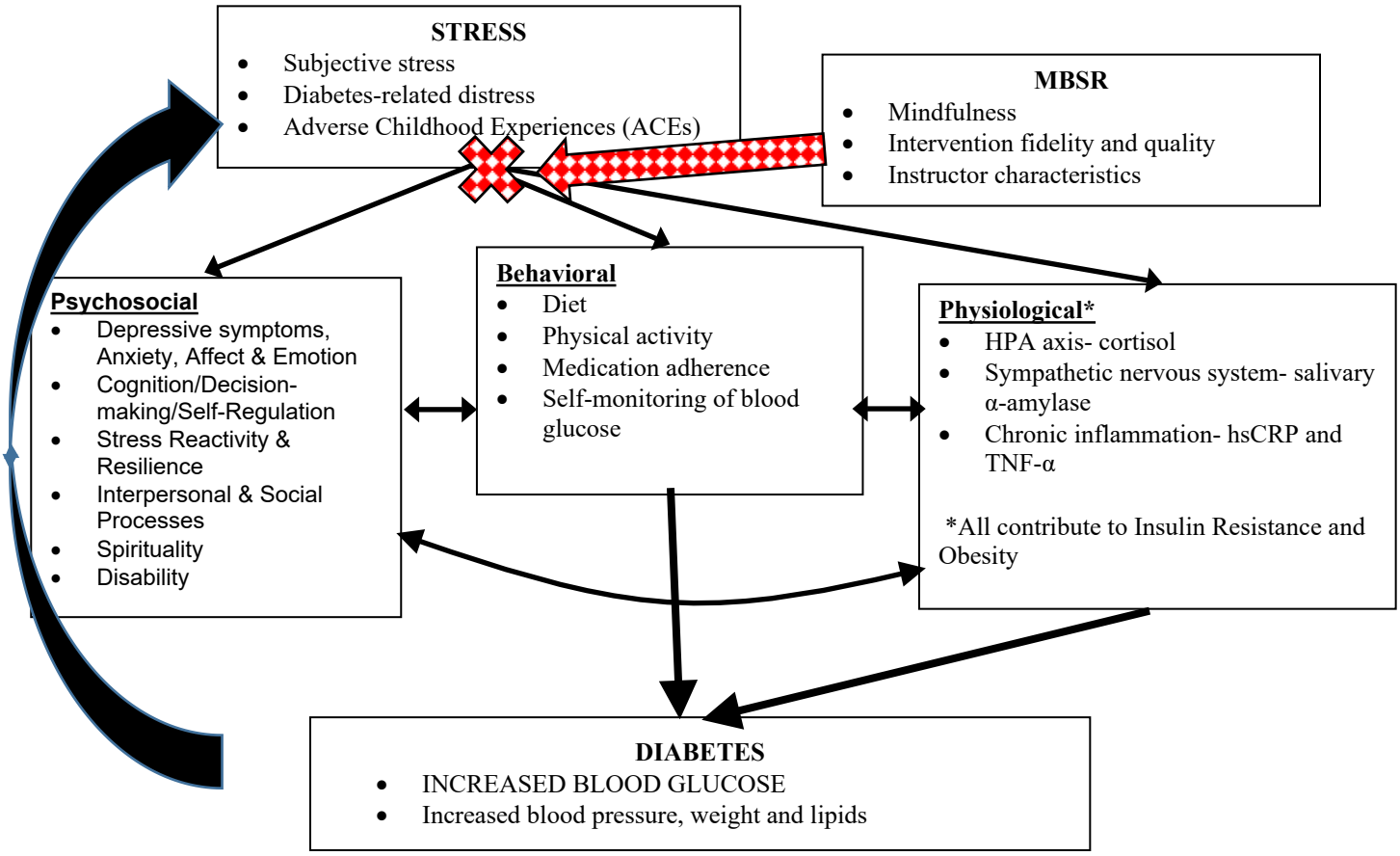
Diabetes is a serious public health problem that affects nearly 30 million people in the U.S. (Center for Disease Control and Prevention, 2017; American Diabetes Association, 2013). Stress is present in 45% of patients with diabetes (Nicolucci et al., 2013), and related to significantly worse glucose control, medication adherence, unhealthy lifestyle behaviors, and reduced quality of life (Hackett & Steptoe, 2017; Crump et al., 2016; Curry, 2016; Downs & Faulkner, 2015; Kelly & Ismail, 2015; Steptoe, 2016; Siddiqui et al., 2015; Fisher et al., 2010; Aikens, 2012; Hessler et al., 2014). Additionally, there is a high prevalence of stress-related conditions in diabetes, including 8.7-17.6% prevalence of depression (Ali et al., 2006; Vancampfort et al., 2015), 20% increased risk of anxiety disorder, and 48% increased risk of anxiety symptoms (Smith et al., 2013). This is significant because managing a chronic disease like diabetes is stressful, and perceived stress, subclinical psychological distress, and diabetes-related distress, can all adversely affect outcomes in diabetes (Hackett & Steptoe, 2017). Several national and

international guidelines recognize the adverse effects of stress on diabetes (Barnard et al., 2012). However, implementation of effective stress reduction strategies for diabetes remains a widespread challenge as no stress reduction intervention to date has been shown to definitively and consistently lower blood glucose (Barnard et al., 2012).

The current standards of care for diabetes include pharmacologic treatment and lifestyle management (American Diabetes Association, 2019a). Lifestyle management includes Diabetes Self-management Education and Support (DSMES), medical nutrition therapy (MNT), physical activity, smoking cessation counseling, and psychosocial care. However, mindfulness-based interventions are not specifically included in the standards of care for diabetes.

Figure 1 demonstrates a comprehensive model of the biological pathways by which stress potentially contributes to poor glucose control and diabetes. This project will assess the effects of MBSR on a meaningful subset of these constructs in adults with uncontrolled diabetes. The study intervention, MBSR, is available to the patient without taking part in the study.

Figure 1. Overview of the biological pathways by which stress potentially impacts diabetes.



If the proposed aims are achieved and MBSR improves glucose control in patients with diabetes, it could transform diabetes treatment by supporting the inclusion of MBSR in the standards of care for diabetes so that patients are empowered with skills for strengthening their internal resources, reducing stress reactivity, and building resilience in the face of a chronic disease like diabetes, which are all essential for implementing healthy behaviors and improving self-management of diabetes. Finally, if longer-term MBSR is found to be beneficial in patients with diabetes, it could have a broader impact and also be

beneficial in patients with other chronic diseases that have also been linked with increased stress and adverse health outcomes.

2.2 Previous Data

We completed a pilot RCT of MBSR compared to health education in 86 overweight or obese women with high subjective stress (mean Perceived Stress Scale-10 score of 22.2), including women with type 2 diabetes and prediabetes. As demonstrated in **Figure 2**, we found a significant reduction in fasting glucose in the MBSR group that was not seen in the health education control group [MBSR group: at 8 weeks -8.9 mg/dl, P = 0.02; at 16 weeks -9.3 mg/dl, P = 0.02] (Raja-Khan et al., 2017). The reason for the reduced fasting glucose in the MBSR group remains unclear. There were no changes in weight, salivary cortisol, or insulin resistance to explain the reduction in glucose. One possible explanation is that the increased mindfulness and decreased perceived stress could have made it easier for the MBSR group to adhere to the diet and exercise guidelines prescribed.

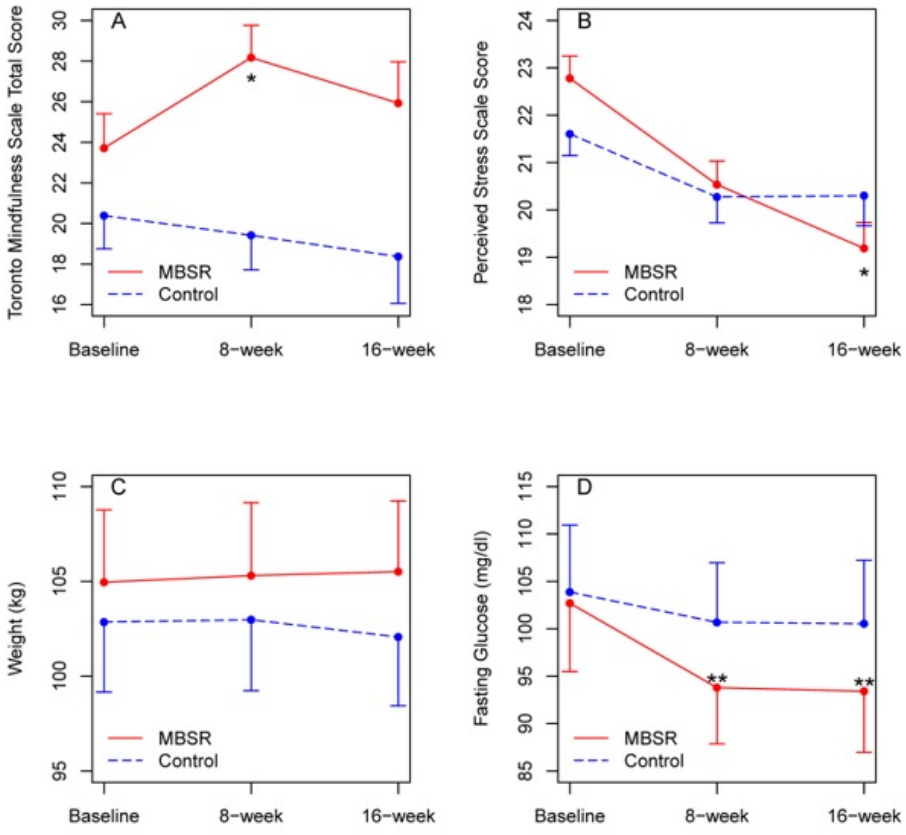


Figure 2. Changes in mindfulness, perceived stress, weight, and fasting glucose in 86 overweight or obese women randomized to MBSR (solid red line) or health education control (dashed blue line). Data are presented as means and SE. *Between-group change from baseline $P < 0.05$. ** Within-group change from baseline P < 0.05. All analyses are by intention-to-treat.[11]

A recent systematic review of mindfulness-based interventions in diabetes showed that four of seven studies successfully lowered HbA1c levels (Noordali et al., 2017). Previous randomized studies of mindfulness-based interventions in diabetes are limited by small sample size, short duration of intervention, and lack of active control, long-term follow-up, and rigorous assessment of intervention fidelity and quality and instructor characteristics as shown in **Table 1** (Gregg et al., 2007; Kopf et al., 2014; Miller et al., 2014; Van Son et al., 2014). The standard MBSR program has a duration of only 8 weeks, and is too brief an intervention to determine a significant impact on hemoglobin A1c, which

reflects average glucose control over the past 3 months. A longer MBSR intervention and follow-up is needed to determine the full impact of MBSR in diabetes.

Table 1. Randomized trials of mindfulness-based group interventions in adults with diabetes.

Author, year	Participants	Intervention	Duration of Intervention	Comparator	Is HbA1c a Primary Outcome?	Report intervention fidelity & quality and instructor characteristics?
Gregg, 2007	81 adults with type 2 diabetes	Acceptance and commitment therapy (ACT)	One day workshop of ACT plus diabetes education	Diabetes education only	YES	NO
Kopf, 2014	110 adults with type 2 diabetes and albuminuria	MBSR	8 weeks plus one booster session at 6 months	Treatment as usual	NO	NO
Miller, 2014	52 adults with type 2 diabetes	Mindful Eating Intervention	3 months	Diabetes education	YES	NO
Van Son, 2014	139 adults with type 1 or type 2 diabetes and low emotional well-being	Mindfulness-Based Cognitive Therapy	8 weeks	Waitlist control	NO	NO
Proposed Study	**290 adults with uncontrolled type 1 or type 2 diabetes**	**MBSR extended with monthly boosters**	**6 months including 8-week MBSR**	**Stress Management Education (active control)**	**YES**	**YES**

2.3 Study Rationale

The proposed project uses mindfulness-based stress reduction (MBSR), a well-researched mindfulness-based intervention, to address stress as a critical barrier to glucose control in patients with diabetes. Stress is increasingly being recognized as an important factor contributing to poor glucose control and complications in individuals with diabetes (Hackett & Steptoe, 2017; Crump et al., 2016; Curry, 2016; Downs & Faulkner, 2015; Kelly & Ismail, 2015; Steptoe, 2016; Siddiqui et al., 2015; Fisher et al., 2010; Aikens, 2012; Hessler et al., 2014). **Figure 1** demonstrates a comprehensive model of the biological pathways by which stress potentially contributes to poor glucose control in diabetes. This project will assess the effects of MBSR on a meaningful subset of these constructs in adults with uncontrolled type 1 or type 2 diabetes. Although the etiological mechanisms underlying type 1 and type 2 diabetes are different, and individuals with type 2 diabetes have greater pancreatic beta cell reserve, the clinical manifestations and stressors of type 1 and type 2 diabetes are similar. Therefore, both adults with type 1 diabetes and adults with type 2 diabetes are likely to benefit from MBSR.

Mindfulness is among the top 50 priority topics for comparative effectiveness research recommended by the Institute of Medicine (2009). A comparative effectiveness review concluded that “Meditation programs, in particular, mindfulness programs, reduce multiple negative dimensions of psychological stress." (Goyal et al., 2014). Mindfulness-based stress reduction has been shown to reduce stress in various patient populations (Raja-Khan et al., 2017; Ludwig & Kabat-Zinn, 2008; Merkes, 2010; Nyklicek & Kuijpers, 2008; Burnett-Zeigler et al., 2016). In support of the biological pathways outlined in **Figure 1**, several systematic reviews and meta-analyses suggest that mindfulness based interventions such as MBSR have psychological, behavioral and physiological benefits in patients with chronic diseases (Levine et al., 2017; Rogers et al., 2017; Ruffault et al., 2017; Carriere et al., 2018; O’Reilly et al., 2014). Dispositional mindfulness, an inherent but modifiable trait of the capacity to attend and to be aware of

what is occurring in the present moment, has been inversely linked with obesity, a highly prevalent precursor to type 2 diabetes (Loucks et al., 2016). Mindfulness may be a novel determinant for glucose control in individuals with diabetes as it increases self-regulation and the ability to notice but not act on cravings (Epstein, 1999; Sedlmeier et al., 2012; Brewer et al., 2011; Loucks et al., 2015). Thus, one way MBSR could be helpful in the self-management of diabetes is by limiting the overconsumption of palatable high carbohydrate foods that increase blood glucose. Furthermore, as MBSR decreases stress and positively affects other key psychological factors often overlooked in standard approaches to diabetes, MBSR could significantly impact the clinical picture of diabetes by empowering patients with diabetes to adopt healthier behaviors (diet, exercise, self-monitoring of blood glucose, medication adherence) that improve their glucose control and reduce their risk of diabetes complications. MBSR could have beneficial physiologic effects on the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic nervous system, and chronic inflammation, leading to reduced insulin resistance and improved blood glucose (Davidson et al., 2003; Carlson & Garland, 2005; Carlson et al., 2007; Winbush et al., 2007). MBSR could also exert beneficial effects by altering gene expression (Black & Slavich, 2016; Creswell et al., 2012; Dusek et al., 2008), as well as brain structure and function (Gotink et al., 2016; Mascaro et al., 2015; Muehsam et al., 2017; Santarnecchi et al., 2014). Several of these potential underlying mechanisms may act synergistically to mediate the impact of MBSR in diabetes.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Men and Women
2. Age 18 years or older
3. Diagnosed with diabetes for at least one year
4. Hemoglobin A1c ≥ 7.5% within 12 weeks and 2 days (86 days) before the start of the study intervention (Orientation session)
5. High Subjective stress defined as Perceived Stress Scale-10 score ≥ 12
6. Available for the intervention sessions with reasonable certainty
7. Have a device equipped with internet connection, camera and microphone and willingness to interact with study staff and class instructors virtually/remotely via this platform
8. Must have a Primary Care Provider (PCP)
9. Must have an accessible/active personal e-mail address or be willing to obtain one for study correspondence

3.2 Exclusion Criteria

1. Current suicidality
2. History of, or meets MINI structured interview criteria for bipolar disorder, psychosis, or other significant psychopathology; those with depression or anxiety will be allowed to participate since they are under the care of a PCP.
3. Inpatient admission for psychiatric disorder within the past two years, or ER visit for psychiatric disorder within the past 10 weeks
4. Meets MINI structured interview criteria for Alcohol Use Disorder or Substance Use Disorder (Past 12 months)
5. Inability to read, write or speak English
6. Current enrollment in a stress reduction program, or in any other investigative study
7. Previous participation in a mindfulness-based stress reduction (MBSR) course
8. Pregnant women
9. Have a household member who is currently, or was previously, assigned to study treatment

The following MINI criteria are considered exclusionary under the umbrella of significant psychopathology:

- Manic Episode – Current

- Hypomanic Episode – Current
- Hypomanic Symptoms – Current
- Bipolar I Disorder – Current
- Bipolar I Disorder – Past
- Single Manic Episode – Current
- Bipolar I Disorder with Psychotic Features – Current
- Bipolar I Disorder with Psychotic Features – Past
- Bipolar II Disorder – Current
- Bipolar II Disorder – Past
- Other Specified Bipolar and Related Disorder – Current
- Other Specified Bipolar and Related Disorder – Past
- Alcohol Use Disorder – Past 12 Months
- Substance Use Disorder (Non-Alcohol) – Past 12 Months
- Any Psychotic Disorder – Current
- Any Psychotic Disorder – Lifetime
- Mood Disorder with Psychotic Features – Current
- Mood Disorder with Psychotic Features – Lifetime
- Psychotic Disorder – Current
- Psychotic Disorder – Lifetime
- Major Depressive Disorder with Psychotic Features – Current
- Major Depressive Disorder with Psychotic Features – Past
- Bipolar I Disorder with Psychotic Features – Current
- Bipolar I Disorder with Psychotic Features – Past
- Antisocial Personality Disorder – Lifetime

Women who are pregnant at the time of screening are not eligible to continue in the study. Women who become pregnant any time after screening, will not be allowed to continue in the study.

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Subjects will be removed from the study for safety reasons as described below based on the PHQ-9, pregnancy clinical criteria (history with pregnancy testing as indicated), and PI AE review, or if they withdraw consent.

3.3.2 Follow-up for withdrawn subjects

Subjects will be advised that they may withdraw from the study at any time by writing or calling to inform the PI Dr. Nazia Raja-Khan that they are withdrawing from the research study. At the time of withdrawal, the reason for the withdrawal will be recorded.

4.0 Recruitment Methods

4.1 Identification of subjects

Subjects will be recruited from a variety of sources within and outside our health care systems. One source will be Dr. Raja-Khan's clinical subspecialty practice of Endocrinology, as well as our larger departmental clinical practices of Internal Medicine and Family Medicine at Penn State Health Practice Sites. An Enterprise Information Management (EIM) Design Specification Form will be submitted up to once per month to request data on subjects that meet study criteria. Another source will be subjects who participated in our prior studies and agreed to be contacted again about future studies. Patients will be recruited at the annual Diabetes Fair held at the University Conference Center in November,

Diabetes Support Group meetings held on campus, and at other health fairs and support groups, and community events within and outside our health care system. The study has been posted on StudyFinder and registered at ClinicalTrials.gov. Recruitment will also be done via an official De-stress Study website, ResearchMatch, HealthGrades, social media (Facebook, Reddit, Instagram, etc.), and through means such as posted flyers and generic letters and emails.

4.2 Recruitment process

4.2.1 How potential subjects will be recruited.

Potential subjects will be recruited from Endocrinology, Internal Medicine and Family medicine clinical practices at Penn State Health Hershey Medical Center, as well as from the larger Penn State Health system and nationally. The EIM search will not be limited to those who have been seen by the departmental practice locations. We will potentially recruit PSH patients who meet the eligibility criteria but have no prior relationship with Dr. Raja-Khan or the Department of Medicine. For such patients, in accordance with IRB policy, we will work with the other Departments so that the initial contact, regardless of method, comes from a person who can be expected to be reasonably familiar to the potential research participant, such as a physician or health care provider directly engaged in the patient's clinical care or an acceptable representative or a physician or health care provider from the clinical unit in which the patient has been seen, or a referring physician. We will promote the study by maintaining ongoing contact with the clinical practices, faculty members and residents in our departments, reminding them of the inclusion criteria, importance of the study, etc. We will present the study at staff meetings, and lunch and learns. The study has been posted on StudyFinder and registered at ClinicalTrials.gov.

Participants will be recruited via ResearchMatch. ResearchMatch is an online resource funded in part by the NIH CTSA. It is operated through Vanderbilt and connects researchers with patients. A recruitment message will be uploaded and sent to participants who match the inclusion criteria. Participants will be allowed to accept or reject the invitation. For those that accept, an automated message (via Redcap Survey) will request basic pre-screening information as well as their phone numbers and emails from them. A coordinator will contact those who are preliminarily eligible to participate in the study.

Participants will also be recruited via HealthGrades. Healthgrades CRM (Customer Relationship Management) is a multi-function platform used to identify and communicate with current Penn State Health patients as well as prospective patients from our local coverage communities. Electronic Medical Record data is securely provided and Healthgrades adds publicly available consumer health data to provide us with a databank which we can utilize to target prospective patients in need of specific healthcare services. Predictive modeling and known diagnoses data combine to enable identification of and messaging to the populations most related to the service line seeking additional patients. Email, direct mail, and search engine marketing are employed to engage patients and invite them into the Penn State Health system.

A Facebook page template has been made to be added to the official Penn State College of Medicine Facebook page and for multiple Diabetes Facebook pages, such as: American Diabetes Association, Diabetes Action Research and Education Foundation, Diabetes Research Institute Foundation, and American Diabetes Association-DiabetesPro. The Facebook page template will also be used for Facebook groups, for example: Type 1 Diabetes Support Group (the One And Only Original), Women's Support Group for Type 1 Diabetes, Diabetes Strong Community, Type 2 Diabetes Friends, Diabetic Support Group, Physician Moms Group (PMG), and others. The study team may find additional groups and pages to post in beyond these examples. Study team

members will first message group moderators and ask them to post on behalf of the study team, ensuring it is clear that it is IRB-approved content and cannot be altered.

Posts will be made about this study in specified "subreddit" communities, with approval from the subreddits' moderators. Examples of specific subreddits the study team will request to post in are: r/diabetes, r/diabetes_t2, r/diabetes_t1, r/Type1Diabetes, and r/type2diabetes. The study team may find additional subreddits to post in beyond these examples. An official De-stress Study website will be used to serve as a landing page for digital recruitment efforts.

Research flyers will be posted throughout HMC campus, Penn State Health practice sites and will be distributed at Diabetes Support Group meetings and Diabetes Education Classes. Flyers will also be posted at pharmacies, community partner sites (e.g. PSH Community Health Needs Assessment (CHNA) forum registrants, etc.), hospitals (e.g. York Hospital, Lancaster General Hospital, etc.), clinics (e.g. WellSpan, Allegheny Health Network, UPMC, private practices, etc.), senior homes, and other healthcare facilities outside of Penn State Health after receiving permission to post flyers. We will also recruit subjects at the Diabetes Fair and The Diabetes Symposium held every November. We will also post the study flyer on the Lion's Eye TV screens. We will promote the study on Penn State University newswires and in newsletters such as the PaTH to Health: Diabetes Newsletter.

Once data on subjects that meet study criteria is extracted from the EIM, emails and/or letters will be sent out to potential subjects using a generic template. Providers (physicians, nurse practitioners, physician assistants, diabetes educators, etc.) will also be reached via a general email template and/or Doximity to inform them of our study.

Potential subjects who may be interested will be put in contact with the research coordinator. We will track all contact from subjects interested in the study. We will develop a pre-screening list that documents date and point of contact, eligibility based on telephone or in-person pre-screening and follow-up if the subject meets prescreening and is interested in participation. Available medical records will be reviewed during the pre-screening assessment to verify recruitment of subjects that meet the medical record-applicable inclusion/exclusion criteria, when possible.

The consent process will take place in-person or via videoconferencing at the screening visit, which will be scheduled during the pre-screening assessment (conducted via a phone call or in-person) if the subject is interested in and eligible for the study at the time of the pre-screening assessment. The consent form document will be emailed or mailed to potential subjects prior to the screening visit to provide ample time for the subjects to review it prior to the screening visit. Consent will be obtained by the research coordinator, not the subject's physician. Potential subjects will be reassured that choosing not to participate will not jeopardize their medical care.

4.2.2 Where potential subjects will be recruited.

Potential subjects will be recruited from Penn State Health Practice Sites including Endocrinology, Internal Medicine, and Family Medicine clinical practices. Subjects will be recruited at the annual Diabetes Fair held at the University Conference Center and at the Diabetes Support Group meetings held on campus and at off site Penn State Health sites. Flyers will be posted at pharmacies, community partner sites (e.g. PSH Community Health Needs Assessment (CHNA) forum registrants, etc.), hospitals (e.g. York Hospital, Lancaster General Hospital, etc.), clinics (e.g. WellSpan, Allegheny Health Network, UPMC, private practices, etc.), senior homes, and other healthcare facilities outside of Penn State Health. The study will also be posted on StudyFinder and registered at ClinicalTrials.gov. Potential subjects will also be

recruited via an official De-stress Study website, ResearchMatch, HealthGrades, and social media (Facebook, Reddit, Instagram, etc.).

4.2.3 When potential subjects will be recruited.

We will recruit no more than 520 subjects in order to reach the randomization target of 290 subjects. We expect to reach this target by randomizing 36 subjects by month 30, 72 subjects by month 36, 120 subjects by month 42, 174 subjects by month 48, 230 subjects by month 54, and at least 290 subjects (but no more than 320 subjects) by month 60.

4.2.4 Describe the eligibility screening process and indicate whether the screening process will occur before or after obtaining informed consent. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their eligibility. In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures is approved by the IRB. [*For FDA regulated studies, consent for any screening activities would need to be obtained prior to screening unless specifically waived by the IRB.]*

We will use a telephone or in-person pre-screening form when potential subjects contact in response to the various ways of recruitment. During pre-screening, available medical records will be reviewed to ensure we only recruit those subjects that meet the inclusion/exclusion criteria. During prescreening potential subjects will also be informed of the dates and times of the classes that they could be assigned to and the requirement of home practice. For the purposes of the study, subjects will be told that they are expected to do at least 25 to 30 minutes of home practice per day for 6 out of 7 days per week. Then they will be asked if they are able to participate in the program with reasonable certainty. If a subject thinks they will miss the Orientation, and won't be able to complete a makeup orientation session prior to Class #2, or if they think they will miss more than 2 classes during the first 8 weeks (including Class #1 to 8 and the Retreat), they will be encouraged to wait for another wave/cohort when they are able to make the time commitment. This prescreening process will occur before obtaining informed consent as it will help study coordinators to assess basic eligibility to warrant a screening visit. Informed consent will be obtained in-person or via videoconferencing at the screening visit, which will be scheduled during the pre-screening assessment. Eligibility will be further assessed at the screening visit and baseline visit. Additionally, a randomization phone call will be made within 1 week prior to the Orientation session, and if a subject is no longer available or interested in participating, they will be treated as a screen failure and will not be randomized.

5.0 Consent Process and Documentation

5.1 Consent Process:

Check all applicable boxes below:

☒ **Informed consent will be sought and documented with a written consent form *[Complete Sections 5.2 and 5.6]***

☐ **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent) *[Complete Sections 5.2, 5.3 and 5.6]***

☐ **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception). *[Complete section 5.2, 5.4 and 5.6]***

☐ **Informed consent will not be obtained – request to completely waive the informed consent requirement.** ***[Complete Section 5.5]***

The following checkbox is for all locations EXCEPT Penn State Health and College of Medicine:

☐ **Exempt Research at all Locations Except Penn State Health and the College of Medicine: If you believe that the research activities outlined meet one or more of the criteria outlined in "HRP-312- Worksheet- Exemption Determination." Please verify by checking this box that if conducting an exempt research study, the consent process will disclose the following (all of which are included in "HRP-590- Consent Guidance for Exempt Research"):**

Penn State affiliation; name and contact information for the researcher and advisor (if the researcher is a student); the activities involve research; the procedures to be performed; participation is voluntary; that there are adequate provisions to maintain the privacy interests of subjects and the confidentiality of the data; and subjects may choose not to answer specific questions.

If the research includes the use of student educational records include the following language in this section (otherwise delete): The parent or eligible student will provide a signed and dated written consent that discloses: the records that may be disclosed; the purpose of the disclosure; the party or class of parties to whom the disclosure may be made; if a parent or adult student requests, the school will provide him or her with a copy of the records disclosed; if the parent of a student who is not an adult so requests, the school will provide the student with a copy of the records disclosed.

Note: If this box has been checked, skip the remainder of section 5 and proceed to section 6 of this protocol. If the investigator's assessment is inaccurate, an IRB Analyst will request revision to the protocol and that an informed consent form be submitted for review and approval. Except for exemptions where Limited IRB Review (see "HRP-312- Worksheet- Exemption Determination") is required or where otherwise requested by the IRB, informed consent forms for research activities determined to be exempt without Limited IRB Review are generally not required to be submitted for review and approval by the University Park IRB.

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

A subject who qualifies for further screening at the time of the pre-screening assessment will be scheduled for the screening visit at the CRC at Hershey Medical Center within 10 weeks and 2 days (72 days) before the start of the study intervention (within 72 days before the Orientation session for each cohort/wave). If the screening visit cannot be conducted in the CRC due to COVID-19, or at the preference of the subject, a Penn State Health (PSH) Teams meeting will be set up and patients will be consented remotely with a witness to the consent on the PSH Teams session. A blank PDF copy of the most currently approved Informed Consent will be emailed to the subject prior to the Screening PSH Teams Meeting. During the scheduled Screening PSH Teams Meeting, the study team will send the participant an email with a link to the eConsent survey. This email will also contain a confirmation of the scheduled date and time to consent the potential participant along with another blank PDF copy of the consent for the potential participant to review. At this time the study team member will direct the potential participant to open the previously sent eConsent survey link, which can be opened on any device that has access to the internet. The consenter will give a brief overview of how to navigate through the eConsent survey (i.e. how to enlarge the font, how to move through each page, and how to save and return). The eConsent process will allow for potential participants to proceed forward or

backward or pause for review later. The Informed Consent will be reviewed with the subject in its entirety, and the subject will be encouraged to ask any questions they may have regarding the study. The study team will instruct the potential participant to answer and complete the questions they will be asked including, do you wish to participate in this study, first name, last name, email address and signature. All of the questions the potential participant will be asked on the eConsent are required and need to be completed prior to the potential participant being able to continue on the next page. The consenter will instruct the participant to add their signature by using their mouse, if on a computer, or finger if using a tablet or cell phone, to sign their name. The optional sections of the study will also be explained by the consenter, and the potential participant will be instructed to check either *Yes* or *No* beside each optional component. After the last optional part, the potential participant must sign their name again. The final step for the participant is to review, certify, and submit the consent form. The participant will be taken to the final page of the eConsent survey, which will allow them to download a signed copy of the consent and/or send themselves an email with the signed consent with their signatures only. To complete the eConsent process, the consenter will sign the consent survey by adding their signature to the relevant sections, which automatically generates a merged signed eConsent file. The consenter will download the completed signed consent and send this completed eConsent form to the study participant via email.

If the potential participant requires a physical copy of the consent to obtain their consent for any reason, it will be mailed several days prior to the Consent PSH Teams Visit. A PSH Teams meeting will be set up and patients will be consented remotely with a witness to the consent on the PSH Teams session. A blank PDF copy of the most currently approved Informed Consent will be emailed to the subject prior to the Consent PSH Teams Meeting. During the Consent PSH Teams Meeting, the consenter will explain in-detail all aspects of the study procedures, review the entirety of the consent, and allow for multiple opportunities to ask questions. The subject will sign the consent, witnessed by the Research Coordinator when the participant is instructed to hold up the consent to the camera for verification after each signature. The subject can return the signed consent to the study team via regular mail, fax, or secure email. No study procedures will be performed, and no Screening PSH Teams Visit will be done, until the study staff has the subject's signed consent in hand.

At the Screening Visit in-person at the CRC, the consent process will take place in a private room setting and prior to any study procedures. The subject will initially be counseled about the purpose of the study, the procedures, the risks, and the time commitment. Voluntariness will be stressed and ample time will be given for discussion and questions. Informed consent is obtained in person, or via PSH Teams, by study personnel, and the subject also has the opportunity to interact with one of the study investigators who reviews eligibility criteria. All subjects give written informed consent to participate in the study during this screening visit and will be given a copy of the signed document, or have the option to be emailed or mailed a copy of the signed document if the consent takes place via PSH Teams.

5.2.2 Coercion or Undue Influence during Consent

The study team will stress voluntariness of participation in the research study. Consent will be obtained by the research coordinator, not the subject's physician. Potential subjects will be reassured that choosing not to participate will not jeopardize their medical care.

5.3 Waiver of Written Documentation of Consent

Not applicable

5.4 Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).

Not applicable

5.5 Informed consent will not be obtained – request to completely waive the informed consent requirement

Not applicable

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects

Not applicable

5.6.2 Cognitively Impaired Adults

5.6.2.1 Capability of Providing Consent

Not applicable

5.6.2.2 Adults Unable to Consent

Not applicable

5.6.2.3 Assent of Adults Unable to Consent

Not applicable

5.6.3 Subjects who are not yet adults (infants, children, teenagers)

5.6.3.1 Parental Permission

Not applicable

5.6.3.2 Assent of subjects who are not yet adults

Not applicable

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Identifiers will be stored securely within REDCap upon completion of the pre-screening phone call or in-person assessment. These identifiers will be retained as part of the study's pre-screening database securely within REDCap to keep track of duplicate screening events. If the subject does not consent to the storage/retaining of their information during the pre-screening phone call, the interview will be stopped and any collected data, including PHI collected via EIM search, will be deleted from REDCap. Contact information and any applicable data for subjects who consented to the storage of their identifiable contact information for future possible research studies will be retained indefinitely.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Pre-screening efforts could not practicably be conducted without viewing the medical record and hence use/access to PHI.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Partial waiver for recruitment purposes is necessary to review available medical records during the pre-screening assessment to ensure we only recruit those subjects that meet the inclusion/exclusion criteria.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

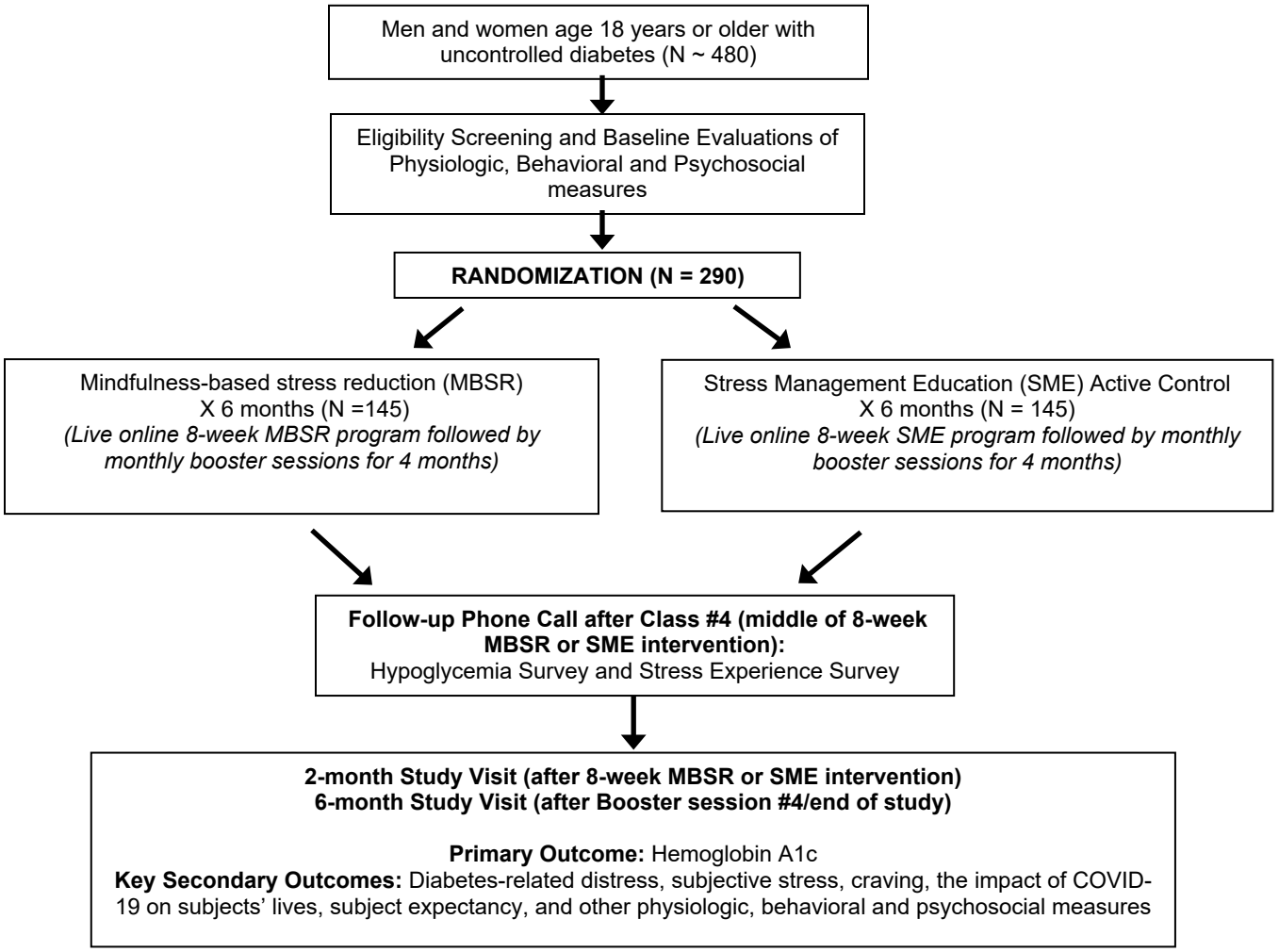
Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

This is a randomized, parallel group two-arm trial that will determine the effects of a 6-month live online MBSR intervention compared to an active control Stress Management Education (SME) on glucose control in 290 adults with uncontrolled diabetes. The proposed 6-month MBSR intervention will consist of the 8-week University of Massachusetts MBSR curriculum (Santorelli et al., 2017), adapted for live online delivery due to the COVID-19 pandemic, followed by live online mindfulness booster sessions every month for 4 months. Subjects will be randomized to one of two groups: (1) MBSR, or (2) SME control. Both MBSR and SME will be delivered online by experienced instructors in a live interactive virtual classroom using videoconferencing. Outcomes will be assessed at baseline, a follow-up phone call after Class #4, and study visits at 2-months and 6-months. If study visits cannot be conducted in person due to COVID-19, or the preference of the subject, study visits will be conducted remotely using videoconferencing and all data that can be collected remotely will be obtained, including the home hemoglobin A1c using the Home A1CNow Self Check kit, urine pregnancy test when applicable, diabetes device data, and surveys. **Figure 3** shows the flow chart of the proposed study.

Figure 3. Flow Chart of Proposed Study



7.2 Study Procedures

7.2.1 PRE-SCREENING procedures

We will use a pre-screening script when engaging with potential subjects via phone or in-person for preliminary assessment of study eligibility for the first time. During pre-screening, available medical records will be reviewed to verify inclusion/exclusion criteria are met (in addition to self-report), whenever possible. Potential subjects will be informed of the dates and times of the classes for the upcoming cohort/wave, and of the requirement of home practice. For the purposes of the study, subjects will be told that they are expected to do at least 25 to 30 minutes of home practice per day for 6 out of 7 days per week, and respond to an email survey once a day about their stress level, food cravings, and home practice (See Pre-Screening Phone call script). The subject will be counseled about the purpose of the study, the procedures, the risks, and the time commitment. The research coordinator will verify that the subject is available for the intervention sessions with reasonable certainty, and that they have a device (e.g. tablet, computer, laptop or smartphone) with internet connection, camera and microphone for participation in the live interactive videoconferencing (Zoom) sessions. If a subject thinks they will miss the Orientation, or if they think they will miss more than 2 classes during the first 8 weeks (including Class #1 to 8 and the Retreat), they will be encouraged to wait for another wave/cohort when they are able to make the time commitment. This prescreening process will occur before obtaining informed consent as it will help study coordinators to assess basic eligibility to warrant the scheduling of a screening visit where informed consent will be obtained in-person or via videoconferencing. A copy of the consent form and the Class Schedule and Homework (class dates/times and required number of minutes of Homework will be the same for both groups) will be mailed/emailed to the subject so they can review it at home prior to the screening visit (See Class Schedule and Homework).

7.2.2 Visit #0 (SCREENING VISIT and procedures)

After eligibility and interest has been assessed during prescreening (via phone or in-person), a screening visit is scheduled at the Clinical Research Center (CRC) at Hershey Medical Center within 10 weeks and 2 days (72 days) before the start of the study intervention (within 72 days before the Orientation session). If the screening visit cannot be completed in the CRC due to COVID-19, or the preference of the subject, the screening visit will be completed remotely using videoconferencing (PSH Teams), and all data that can be collected remotely will be obtained. The screening visit will last approximately 2 hours. Subjects will be asked to bring their diabetes devices (glucometers, continuous glucose monitor (CGM), insulin pump and other smart insulin delivery devices) to their remote or in-person screening visit so that the dates and times on these devices can be verified. If the subject does not have a glucometer, a letter will be sent to their primary care provider, PCP, asking them to prescribe a glucometer for the patient, and to refer the patient to a diabetes educator for glucometer teaching if the patient has never used a glucometer before. This is being done because it is the standard of care for patients with uncontrolled diabetes, and it is important to collect historical blood glucose levels on subjects for data analysis, before and after the subject attends stress management classes. Subjects will be able to obtain a glucometer with their physician's prescription, and get the necessary education on its use. Subjects will NOT be excluded from the study if they don't have a glucometer or obtain one during the course of the study.

During the screening visit, written informed consent to participate in the study will be obtained in person, or remotely via PSH Teams, by the research coordinator. Informed consent will be obtained only after subjects are given sufficient information about the research, procedures and expectations, and the risks and benefits to reach an informed decision as to whether they will voluntarily participate. As MBSR could have potential adverse effects, subjects will be made

aware that the study treatment they are assigned to could have adverse effects, including increased depression, anxiety or panic, re-experiencing of traumatic memories (especially if there is a history of trauma or PTSD), dissociation, executive dysfunction, headaches/body pain and insomnia (Lindahl et al., 2017; Lomas et al., 2014; Cebolla et al., 2014; Brooker et al., 2013; Johnson et al., 2016; Reynolds et al., 2017; Britton et al., 2010). The subject will have the opportunity to interact with one of the study investigators, who reviews the eligibility criteria.

Subjects will be given a copy of the Class Schedule and Homework. This will list the dates and times for all the classes that they could be assigned to and the requirement of at least 25 to 30 minutes of home practice per day for 6 out of 7 days per week. The research coordinator will verify that the subject is available for the intervention sessions with reasonable certainty. If a subject thinks they will miss the Orientation, or if they think they will miss more than 2 classes during the first 8 weeks (including Class #1 to 8 and the Retreat), they will be encouraged to wait for another wave/cohort when they are able to make the time commitment.

After obtaining informed consent, further screening will be completed during the screening visit (See Screening Assessments Form). Subjects will complete the Perceived Stress Scale-10 (PSS-10) questionnaire and need a score ≥ 12 to continue in the study. This cutoff is based on normative data from the U.S. population (Cohen & Williamson, 1988). The PSS-10 will be self-administered in REDCap and reviewed by the study coordinator for completeness. REDCap will automatically calculate the PSS-10 score when subjects answer all items on the PSS-10. If any item of the PSS-10 is intentionally skipped, a valid score cannot be calculated to assess inclusion criteria and the subject is ineligible to continue with the screening.

Medical records, when available, will be reviewed to confirm that the subjects have diabetes and are eligible for the study.

Demographics: Age (calculated from date of birth), Sex (male or female), Race and Ethnicity will be recorded at screening.

Screening Laboratory Exam: Subjects will present to the Penn State Clinical Research Center (CRC) for the screening visit. They will not need to fast for the screening visit. A maximum of 30 mL of blood will be taken during the screening visit to assess hemoglobin A1c for eligibility. (**Table 2**). If the patient has a lab hemoglobin A1c within 12 weeks and 2 days (86 days) before the start of the study intervention (Orientation), these records may be obtained, and after verifying the hemoglobin A1c result in the outside records or the EMR, the hemoglobin A1c result can be accepted in lieu of repeating the test for screening. If the screening visit is being conducted remotely due to COVID-19, or due to the preference of the subject, and if a lab HbA1c value collected within the 12-week window is not available in their medical record, then the subject will be mailed a Home A1CNow Self Check kit, and sent instructions and a link to a video demonstration on how to perform the blood test. For subjects with the Penn State Health care region, who do not have an hemoglobin A1c in their EMR, they will be given the option to have a lab sample obtained at a Penn State Health center to assess hemoglobin A1c or have a Home A1CNow kit mailed to them. The coordinator will observe and guide them through the appropriate collection steps during the (PSH Teams) live videoconferencing screening visit. Subjects will communicate their home hemoglobin A1c test result to the study team by showing the research coordinator their home hemoglobin A1c result as displayed on their Home A1CNow Self Check kit during the (PSH Teams) live videoconferencing screening visit.

Pregnancy clinical criteria (history with pregnancy testing as indicated): As the study interventions pose no risk to a developing pregnancy, and the rationale for excluding pregnant women is that pregnancy may affect blood glucose, clinical criteria (history with pregnancy

testing as indicated) will be used for exclusion. There is minimal clinically relevant change in blood glucose in the early first trimester, lessening the potential impact of early pregnancy on study outcomes. For research purposes in this protocol, women are not considered of childbearing potential if they

(1) Have completed menopause, defined as
   a. Age greater than 55 years old, OR
   b. Age 55 years or less and at least 12 months since last menstrual period, OR
   c. Age 55 years or less and at least 6 months since last menstrual period and FSH > 40 IU

(2) Have had a surgical sterilization defined as
   a. Hysterectomy and/or
   b. Bilateral salpingectomy and/or
   c. Bilateral oophorectomy

(3) Do not have a male partner who can father children; Male partners can be incapable of fathering children because of congenital anomalies, surgery, or medical treatment.

In all other women, pregnancy testing will not be indicated when there is reasonable certainty that the woman is not pregnant defined as meeting any one of the following criteria recommended by the CDC (CDC, 2021). These criteria have a negative predictive value of 99%–100%, which means that they are highly accurate in ruling out pregnancy among women who are not pregnant. If a woman meets any one of these criteria, there is reasonable certainty that she is not pregnant, and a urine pregnancy test will not be indicated for the purpose of this study:

- is ≤7 days after the start of normal menses
- has not had sexual intercourse since the start of last normal menses
- has been correctly and consistently using a reliable method of contraception
  - oral contraceptives
  - injectables
  - barrier methods
  - intrauterine device (IUD)
  - hormonal implant
  - hormonal ring/patch
  - bilateral tubal ligation
  - partner with vasectomy
- is ≤7 days after spontaneous or induced abortion
- is within 4 weeks postpartum
- is fully or nearly fully breastfeeding (exclusively breastfeeding or the vast majority [≥85%] of feeds are breastfeeds), amenorrheic, and <6 months postpartum

If a woman does not meet at least one of the above criteria, then urine will be collected for a pregnancy test, and any subjects found to be pregnant will be informed of their pregnancy test results, and then excluded from the study due to the effects of pregnancy on study outcomes. If the subject has a pregnancy test within 2 weeks before the screening visit, documented in their medical records, these records may be obtained, and after verifying the pregnancy test result in the outside records or the EMR, the pregnancy test result can be accepted in lieu of repeating the test for screening. If the screening visit is conducted remotely, and if a pregnancy test result collected within 2 weeks before the screening visit is not available in the subject's medical record, then the subject will be mailed a urine pregnancy test. Subjects will communicate their urine pregnancy test result to the study team by showing the research coordinator their pregnancy test result as displayed on their urine pregnancy test kit during the (PSH Teams) live

videoconferencing screening visit. Subjects found to be pregnant will be excluded from the study.

Screening Safety Questionnaire: Subjects will be screened for depression and suicidality using the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 will be self-administered in REDCap and reviewed by the research coordinator for completeness.

If a subject is not comfortable with answering the 9th item of the PHQ-9 at the screening visit, they will be excluded from the study. If a subject refuses to answer the 9th item of the PHQ-9 at any of the subsequent study visits, the subject will be excluded from the study, and the research coordinator will immediately contact one of the below suicidality experts.

PHQ-9 scores will be calculated in REDCap, even if subjects refuse to answer all of the PHQ-9 questions. If a subject's PHQ-9 score at any of the study visits is 10 or greater, they will be advised to see their PCP for further evaluation. The research coordinator will give the subject an Incidental Findings Letter to share with their PCP. This letter will include the subject's PHQ-9 score. These subjects can still continue in the study as long as they meet the other eligibility criteria.

If a subject scores 1 or greater on the 9th item of PHQ-9, the research coordinator will interview the subject using the modified P4 Screener to assess suicide risk (Dube et al., 2010). If the subject answers 'Somewhat Likely' or 'Very Likely' to the modified P4 Screener question which asks "How likely do you think it is that you will act on these thoughts about hurting yourself or ending your life some time over the next month?", they are considered higher risk and will not be eligible for the study. For these higher risk subjects, the research coordinator will immediately contact one of the following appropriate suicidality experts to initiate a psychiatric consultation:

1. Dr. Dahlia Mukherjee (cell 775-351-9927)
2. Dr. Erika Saunders (pager 2292, cell 717-514-3818)
3. Other personnel available for an immediate Psychiatric consult

If on the modified P4 Screener, the subject answers 'Not at all Likely' to "How likely do you think it is that you will act on these thoughts about hurting yourself or ending your life some time over the next month?" and they answer 'No' to "Is there anything that would prevent or keep you from harming yourself?", a follow-up prompt is triggered "What is preventing you from acting on harming yourself?" If the subject provides a response, they are eligible to continue in the study as long as they meet the other eligibility criteria. If the subject cannot/does not provide a response, the subject will be considered higher risk and will be excluded from the study. The research coordinator will immediately contact one of the above suicidality experts.

MINI structured interview: Screening will also include the MINI International Neuropsychiatric Interview (MINI) Version 7.0.2., which is a brief structured interview for the major psychiatric disorders in DSM-V and ICD-10 (Sheehan et al., 1998; Sheehan et al, 1997; Lecrubier et al., 1997; Amorim et al., 1998). The MINI assesses for the 17 most common disorders in mental health that are the most important to identify in clinical and research settings. MINI interviews will be conducted by a trained research coordinator under the supervision of a clinical psychologist (Dr. Mukherjee) to screen patients for psychiatric conditions.

The MINI will be used for research purposes to document whether subjects meet criteria for psychiatric conditions, not to make any clinical diagnoses. Subjects will not be informed of the results of their MINI. If the MINI indicates that the subject meets criteria for any of the excluded conditions (See Exclusion Criteria above), the subject will not be eligible for the study. All excluded subjects will be given a list of General Resources for diabetes and mental

health so as not to imply the reasons for which they were excluded from the study. This list will be mailed to excluded subjects when screening visits are completed remotely.

Section B of the MINI, which screens for suicidality, will not be completed as subjects will have already been screened for suicidality with the PHQ-9 and if indicated the modified P4 Screener as described above.

The MINI Summary and select outcomes from the body of the MINI (e.g. Severity of Binge-Eating Disorder) will be entered into REDCap by the study coordinator. These results will be used to characterize the study population.

The completed paper MINI will be kept in the subject's study folder.

Participating in this research study will not deny any appropriate medical care or mental health care subjects would ordinarily receive from their PCP, mental health provider, or other health care providers. Names and doses of both diabetes and psychiatric medications will be collected throughout the study.

At the end of the screening visit, if the subject remains eligible to continue in the study, the subject will be scheduled for a baseline study visit and the following additional procedures will be completed at the screening visit:

- The research coordinator will ensure that the dates and times on the subject's diabetes devices (glucometers, CGM, insulin pump and other smart insulin delivery devices) are correct in anticipation of collecting data from these devices at the subsequent study visits. The research coordinator will record the date and time that are on each device. If the date or time on a device are not correct, the research coordinator will record the device date and time offset, and work with the subject to correct the date and time on the device. This will be repeated at each of the subsequent study visits. If study visits are conducted remotely, subjects will be asked to communicate the dates, times and other data on their diabetes devices to the study team by sharing their diabetes device data remotely (by uploading or connecting their diabetes device data to secure, cloud-based diabetes management systems such as Dexcom Clarity and LibreView as done in routine clinical care), by sharing reports of their diabetes device data, by showing the the study team their diabetes device displays or reports during the remote (PSH Teams) live videoconferencing study visit, or by self-reporting their diabetes device data via a phone call after the study visit. If the date or time on a device are not correct, the research coordinator will record the device date and time offset, and work with the subject to correct the date and time on the device during the remote (PSH Teams) live videoconferencing study visit. This will be repeated at each of the subsequent study visits.
- Subjects will complete a Phone Call Time Preference questionnaire in REDCap indicating their preferred windows of time to receive phone calls for visits and scheduling appointments. Subjects will be instructed that 3-hour windows of time are preferable (e.g. 6-9 PM on Wednesdays is better as it allows for more flexibility than 8-9AM, 1-2PM, and 5-6PM). Subjects will complete this questionnaire at the screening, baseline and 2-month study visits.
- If the subject does not have a working glucometer, a letter will be sent to their primary care provider, PCP, asking them to prescribe a glucometer for the patient, and to refer the patient to a diabetes educator for glucometer teaching if the patient has never used a glucometer before. This is being done because it is the standard of care for patients with uncontrolled diabetes, and it is important to collect subjects' historical blood glucose levels for data analysis, before and after the study stress reduction sessions. Subjects will be able to obtain a glucometer with their physician's prescription, and get the necessary education on its use. If the subject has had a glucometer previously and does not have one now for any reason (e.g. they lost it, broke it, etc.), they will be

offered a sample glucometer kit (if available), and advised to check with their insurance regarding coverage of additional glucometer testing supplies (e.g. test strips and lancets), and to see their PCP for prescriptions for additional glucometer testing supplies. The research coordinator will work with the subject to ensure that the correct date and time are set on the sample glucometer they are given. Subjects will be asked to bring their sample glucometer to their subsequent remote or in-person study visits so that data can be collected from them. Subjects paying out of pocket for glucometer testing supplies will be advised to consider Walmart's ReliOn brand testing supplies which are more affordable. This will be repeated at the baseline and 2-month study visits, when applicable. Subjects will NOT be excluded from the study if they don't have a glucometer or obtain one during the course of the study.

- Subjects will be given information about the optional 24-hour diet recall surveys they will be invited to complete during the 2 weeks before Class #1, 2 weeks after Class #8, and 2 weeks before Booster #4. Dietary intake data for 24-hour recalls will be collected and analyzed using the Automated Self-Administered 24-hour (ASA24) Dietary Assessment Tool, version 2020 and version 2022, developed by the National Cancer Institute, Bethesda, MD (https://epi.grants.cancer.gov/asa24). The research coordinator will send subjects unannounced emails with a link to complete their 24- hour diet recall on the ASA24 website. The emails will be sent during the specified time windows to collect 24-hour diet recall data for 1 weekday and 1 weekend around the baseline, 2-month and 6-month study visits.
- The subject will be given or mailed the Baseline Medical History questionnaire to complete at home. They will complete this electronically or on paper. If they complete a paper form, they will be asked to mail it back. They can also bring the paper form to their baseline visit if it is being done in the CRC.
- The subject will be given written instructions and reminders for their baseline study visit.

Table 2. Screening assessments

Inclusion/Exclusion assessments	Safety assessments
-Hemoglobin A1c ≥ 7.5% -Pregnancy clinical criteria with pregnancy testing as indicated (in females age 55 years old or younger) -Perceived Stress Scale-10 score ≥ 12	-PHQ-9 -modified P4 Screener if 9th item of PHQ-9 is 1 or greater -MINI structured interview

Overview of Study Visit Time Windows (See Table 3): The screening visit will be scheduled within 10 weeks and 2 days (72 days) before the start of the study intervention (Orientation session). The baseline study visit will be scheduled within 6 weeks and 2 days (44 days) before the Orientation session (to allow for sufficient time for scheduling around holidays). Randomization will take place during the week before the Orientation session. Class #1 (the first class after Orientation) will start ~1 week after the Orientation session. The follow-up phone call will be scheduled within the 2 weeks after Class #4. The 2-month study visit will be scheduled within the 4 weeks immediately after Class #8 (the end of the 8-week MBSR or SME program). The 6-month study visit will be scheduled within the 4 weeks immediately after Booster session #4. The time windows for capturing the optional 24-hour diet recall data are within 2 weeks before Class #1, 2 weeks after Class #8, and 2 weeks before Booster #4. The time windows for capturing the optional Actigraph data are +/- 2 weeks of the baseline and 2-month study visits, and in the 4 weeks before the 6-month study visit.

It is possible that a subject completes the screening visit, or the screening and baseline visits, for a cohort and then is unable to be randomized to that cohort and needs to wait to be

randomized to a later cohort (due to reaching the maximum number of participants permitted in a class, or due to the subject not being reached in time for randomization, or due to the subject requesting to participate in a later cohort when they will be more available). In these scenarios, the screening and baseline visits will need to be repeated if they fall outside of the Study Visit Windows for the new later cohort. In other words, the screening visit will need to be repeated if it is more than 10 weeks and 2 days (72 days) before the new later Orientation session, and the baseline visit will need to be repeated if it is more than 6 weeks before the new later Orientation session. Subjects will need to attend the screening visit and baseline visit within the specified time window in order to be randomized. In these instances, all data from screens and visits that were collected during times when the subject was not randomized will be maintained. However, only the screening and baseline data provided by the subject within the specified time windows will be used in analysis. Data collected from earlier duplicate screens will be maintained and documented securely in REDCap, therefore it is possible that multiple study ID numbers correspond to one randomized subject.

The research coordinator will make 3 attempts to reach a subject for the follow-up phone call within the 2 weeks after Class #4. If a subject misses the follow-up phone call within this specified 2-week time window, the subject will not be withdrawn from the study, and their follow-up phone call data will be considered missing data. If a subject misses the 2-month study visit within the specified time window, the research coordinator will contact them and if the subject confirms that they are willing to come in for the final 6-month study visit, the subject will not be withdrawn from the study and their 2-month study visit data will be considered missing data.

Lost to Follow-up: Subjects will be withdrawn from the study and considered lost to follow-up if they cannot be reached after doing the following:

- First, the research coordinator will call and e-mail the subject once a week for 3 weeks.
- If no response, then the research coordinator will make 3 attempts to call their emergency contact if they provided an emergency contact. Subjects will be asked to provide an emergency contact at the screening visit in case we cannot reach them because they moved, are in a hospital, etc. The emergency contact is usually someone that does not live with them, or at least someone with a different phone number.

This process will be initiated when the subject has not shown up to a study visit. If no response is received from the subject within 60 days of missing the study visit, the subject will be withdrawn from the study and considered lost to follow-up.

Drop outs/Treatment failures: Dropouts may occur due to participant choice or physician recommendation for reasons such as adverse effects, poor compliance, etc.

If a subject is randomized but misses Orientation, the instructors may offer the subject an individual Orientation session. If the subject is unable to complete Orientation before Class #2 after being randomized, they will not be permitted to continue in the study.

As soon as a subject is determined to be Lost to Follow-up, Withdrawn or Completed, all data collection will cease after collecting reasons for participant-initiated withdrawal on the Attrition Survey. The date a subject is no longer considered part of the study will be documented in an End of Trial form.

Attrition Information: CONSORT guidelines require a reason for dropout for every subject, and whether the reason was due to an adverse event. The research coordinator will collect attrition information for each dropout from the study, and record the dropout date, subjects' responses to Yes/No questions about general reasons for attrition that do not reveal the subjects' group assignment, and whether the dropout is Subject-initiated or Investigator-initiated.

If it is a Subject-initiated dropout or a lost to follow-up, the subject will be e-mailed a link to a REDCap Participant-Completed Attrition Information Survey consisting of one open

ended question to elicit feedback about their experience in the study and learn more about their reasons for not continuing in the study. As subjects' responses could reveal group assignment, the research coordinator and other blinded study team members will be blinded to subjects' responses to this survey in REDCap.

Investigator-initiated withdrawals: A subject may also be withdrawn from the study and/or intervention by the investigator. In this case, the research coordinator will record the reasons why the investigator withdrew the subject from the study (See DSMP).

7.2.3 Visit #1 (Baseline Study Visit)

Enrolled subjects who meet the eligibility criteria at the screening visit will be invited to schedule a baseline study visit at the CRC. If the baseline visit cannot be completed in the CRC due to COVID-19, or the preference of the subject, the baseline visit will be completed remotely using videoconferencing (PSH Teams), and all data that can be collected remotely will be obtained, including the home hemoglobin A1c using the Home A1CNow Self Check kit, urine pregnancy test when applicable, diabetes device data, and surveys. The subject will not participate in hair, nail or saliva collection if visits are remote. The baseline visit will last approximately 3 hours. The baseline visit will be scheduled within 6 weeks prior to the planned start of the study intervention (Orientation session). Eligible subjects who complete the baseline visit can undergo randomization and subsequently attend Orientation. Hemoglobin A1c and Perceived Stress Scale-10 assessments will be repeated at the baseline visit, however subjects will not be excluded at baseline based on the results. The MINI will not be repeated at baseline. Subjects will need to continue to meet the rest of the Inclusion/Exclusion criteria at the baseline visit to be able to continue in the study. An overview of the study procedures is found in **Table 3**.

Subjects will be asked to provide the following for their remote or in-person baseline visit:

- The completed Baseline Medical History questionnaire they were given at the screening visit; They will complete this electronically or on paper. If they complete a paper form, they will be asked to mail it back. They can also bring the paper form to their baseline visit if it is being done in the CRC.
- A list of their current medications and dietary supplements so their current medications and supplements can be recorded
- Their smartphone, if they have one
- Their diabetes devices (glucometers, CGM, insulin pump and other smart insulin delivery devices)
- Home A1cNow Self Check Kit if provided one at screening

The subjects will present to the baseline visit in the CRC in a 10-hour fasting state (no food or drink, except for water). Additionally, subjects will be instructed not to eat or drink (except for water), chew gum, smoke, brush their teeth, exercise physically, or consume prescription or over-the-counter medications in the 60 minutes prior to their baseline visit (as well as during the last 60 minutes of their baseline visit) as we will be collecting saliva samples 1) Just before the study visit starts, and 2) immediately after the study visit ends. If subject forgets to fast, blood will still be drawn and documentation will be made of how many hours it has been since they last had something to eat or drink.

Subjects will be instructed not to wash their hair for 24 hours before their study visit in the CRC and not to have their hair cut to a length less than 2 cm (as we will be collecting *optional* 2 cm hair samples weighing at least 10 mg to assess cortisol levels over the past 2 months). Subjects may opt-out of this procedure and will still be permitted to continue in the study. Subjects will be instructed not to clip their fingernails for at least 2-3 weeks prior to their study visit to allow for the *optional* clipping of approximately 2 mm of nails from each finger of both hands.

Subjects will be instructed to remove any nail polish at least 24 hours before their study visit. Subjects may opt-out of this procedure and will still be permitted to continue in the study.

At the baseline visit, subjects will be given another copy of the Class Schedule and Homework. The research coordinator will verify that the subject continues to be available for the intervention sessions with reasonable certainty. If a subject thinks they will miss the Orientation, or if they think they will miss more than 2 classes during the first 8 weeks (including Class #1 to 8 and the Retreat), they will be encouraged to wait for another wave/cohort when they are able to make the time commitment.

The research coordinator will obtain baseline measures including saliva, blood, hair (optional), and nail (optional) samples for hormonal and metabolic parameters, and a brief physical exam if the baseline study visit is in the CRC.

Self-administered questionnaires will be directly entered into REDCap by all subjects and reviewed by the research coordinator for completeness. Data will be collected from subjects' diabetes devices (glucometers, CGM, insulin pump and other smart insulin delivery devices) if they use these devices.

At the baseline visit, a urine pregnancy test will be administered to female subjects of childbearing potential who do not meet any of the criteria for reasonable certainty of not being pregnant as defined above in the screening visit. Any subjects found to be pregnant will be informed of their pregnancy test results, and then withdrawn from the study due to the effects of pregnancy on study outcomes. If the subject has a pregnancy test within 2 weeks before the baseline visit, documented in their screening visit or verified in their medical records, the pregnancy test result can be accepted in lieu of repeating the test at baseline. If the study visit is conducted remotely, and if a pregnancy test result collected within 2 weeks before the study visit is not available, then the subject will be mailed a urine pregnancy test to complete at this visit. Subjects will communicate their urine pregnancy test result to the study team by showing the research coordinator their pregnancy test result as displayed on their urine pregnancy test kit during the (PSH Teams) live videoconferencing study visit. If the pregnancy test is positive, the subject will be withdrawn from the study.

Subjects will be given a Home A1CNow Self Check kit at baseline, or if they received a kit at screening they will be asked to bring the kit to their remote or in-person baseline visit. If the baseline study visit is conducted remotely, subjects will be mailed the Home A1cNow Self Check Kit. The research coordinator will review procedures and watch instructional videos with subjects, and assist the subjects in obtaining their hemoglobin A1C value from the kit. Subjects who complete their baseline study visit in the CRC will bring this kit home in case, for any reason, they are not able to return to the CRC for their 2 month and 6 month visit so that they will be able to collect their hemoglobin A1C results at home as this is the primary outcome for this study. If the 2 month and 6 month visits are being conducted at the CRC, the subjects will be asked to bring their Home A1CNow Self Check kit to the CRC and the kit will be used to collect their home hemoglobin A1c, in addition to the blood draw for hemoglobin A1c. The Home A1cNow Self Check Kit contains step by step instructions for subjects to reference for future testing.

If the subject opts-in to wearing an Actigraph device, the subject will be given an Actigraph device to wear around their waist for 7 days after the baseline visit. If the study visit is conducted remotely, the subject will be mailed the Actigraph device, with a stamped envelope to return after the required wear time.

Table 3. Overview of Study Procedures and Measurements

Study Procedures	Pre-Screen-ing Phone Call	Study Visit #0 Screening	Study Visit #1 Baseline	Random-ization Phone Call	Start Class #1 of 8-wk MBSR or SME	Study Visit #2 /Follow-up Phone Call	Study Visit #3	MBSR or SME Booster sessions	Study Visit #4 (End of study)
Timeline		Within 10 wks before Orientation	Within 6 wks before Orientation	Within 1 wk before Orientation	~1 wk after Orientation	Within 2 wks after Class #4	After Class #8 (2 months)	Once a month for 4 months	After Booster #4 (6 months)
Phone or In-person Intake Pre-Screen	x								
Written Informed Consent		x							
Class Schedule & Homework- Verify subject availability		x	x	x					
MINI structured interview		x							
Screening Assessments		x	x						
Phone Call Time Preference		x	x				x		
Orientation Questionnaire			x						
Stress Reduction Expectancy Scale (SRES)			x				x		x
Baseline Medical History			x						
Medications			x				x		x
Stress & Cravings Surveys			x	x	x	x	x	x	x
Daily Diary Surveys					x **Start-up after Class #1**	x	x	x	x
GLUCOSE CONTROL AND OTHER PHYSIOLOGIC OUTCOMES									
Primary Outcome: Hemoglobin A1c[a]		x Lab or Home Kit	x Lab & Home Kit				x Lab & Home Kit		x Lab & Home Kit
Fasting Glucose			x				x		x
Glucometer/CGM/ insulin pump data		**Date/Time check only**	x				x		x
C-peptide (for HOMA-IR)			x				x		x
Fasting Lipids, hsCRP & TNF-α			x				x		x
Saliva cortisol & α-amylase			x				x		x
Blood pressure & Heart rate			x				x		x
Weight, Height, and Waist and Hip Circumference			x				x		x
Body composition (Tanita scale measurements only – if in CRC)			x				x		x
Hair and nail samples (optional)			x				x		x
Urine pregnancy test		x	x				x		x
Hypoglycemia Survey			x			x	x		x
BEHAVIORAL OUTCOMES									
24-hour dietary recalls (optional)			x				x		x
Food Craving Questionnaire-Trait Reduced			x				x		x
Walking Enjoyment			x				x		x
Accelerometer data (optional)			x				x		x

Adherence to diabetes medications (Participant Questionnaire)			x				x		x
Counterfactual Measurement			x						x
PSYCHOSOCIAL OUTCOMES									
Toronto Mindfulness Scale (TMS)			x				x		x
Perceived Efficacy, Satisfaction, Engagement & Confidence							x		x
Diabetes Distress Scale			x				x		x
Perceived Stress Scale-10 (PSS-10)		x	x				x		x
Short Form-12 (SF-12)			x				x		x
Positive and Negative Affect (PANAS)			x				x		x
BRFSS (ACE survey)			x						
Childhood Trauma (CTQ)			x						
Modified Coronavirus Impact Scale			x				x		x
GAD-7			x				x		x
PROMIS Sleep Disturbance 8a			x				x		x
Safety screens (PHQ-9, and if indicated modified P4 Screener)		x	x				x		x
Stress Experience Survey			x			x	x		x

[a] Screening hemoglobin A1c: If the patient has a lab hemoglobin A1c result within 12 weeks and 2 days (86 days) before the start of the study intervention (Orientation), these records may be obtained, and after verifying the lab hemoglobin A1c result in the outside records or the EMR, the lab hemoglobin A1c result can be accepted in lieu of repeating the test for screening. If the patient does not have a lab hemoglobin A1c result within 12 weeks and 2 days (86 days) before the start of the study intervention, the screening hemoglobin A1c result will be obtained from either the Hershey Clinical Lab (if the screening visit is conducted in person), or from a Home A1cNow Self Check Kit (if the screening visit is conducted remotely).

In-person baseline, 2-month, and 6-month study visit hemoglobin A1c: When the baseline, 2-month, and 6-month study visits are conducted in person, hemoglobin A1c results will be obtained from both the Hershey Clinical Lab and from the Home A1cNow Self Check Kit. A lab hemoglobin A1c result obtained from the Hershey Clinical Lab within 2 weeks before the visit can be accepted as the study visit lab hemoglobin A1c. A screening Home A1cNow Self Check Kit hemoglobin A1c result within 2 weeks before the baseline visit can be accepted as the baseline home hemoglobin A1c.

Remote baseline, 2-month, and 6-month study visit hemoglobin A1c: When the baseline, 2-month, and 6-month study visits are conducted remotely, home hemoglobin A1c will be collected using the Home A1cNow Self Check Kit. A screening Home A1cNow Self Check Kit hemoglobin A1c result within 2 weeks before the baseline visit can be accepted as the baseline home hemoglobin A1c. If the subject has a lab result (e.g. lab hemoglobin A1c) outside of the study, the lab result (e.g. lab hemoglobin A1c) will be recorded as the study visit lab result (e.g. lab hemoglobin A1c) after verifying the result in outside records or the EMR.

Missed 2-month and 6-month (in-person or remote) study visits: If the subject misses their 2-month or 6-month study visit, and has a lab result (e.g. lab hemoglobin A1c) outside of the study, the lab result (e.g. lab hemoglobin A1c) will be recorded as the study visit lab result (e.g. lab hemoglobin A1c) after verifying the result in outside records or the EMR.

All subjects will be given the same general written guidelines on diet and exercise at the baseline visit, which will consist of two handouts downloaded from the American Diabetes Association Patient Education Library: (1) "Plan Your Portions" Diabetes Placemat and (2) "The Diabetes Advisor - Physical Activity." All subjects will also be given handouts on Hyperglycemia and Hypoglycemia, as well as Glucometer Best Practices and Blood Glucose Meter Correlation, at the baseline visit. This will be the only information that will be the same across both groups. The MBSR group will not receive any additional health education other than these handouts.

Baseline Laboratory Exam:

Subjects will present to the baseline study visit in the CRC after a 10-hour fast (no food or drink, except for water) for collection of a single sample of blood. Additionally, subjects will be instructed not to eat or drink (except for water), chew gum, smoke, brush their teeth, exercise physically, or consume prescription or over-the-counter medications 60 minutes prior to presenting for their baseline study visit (as well as during the last 60 minutes of their baseline visit) to allow for collection of saliva samples.

In the fasting state, the research coordinator and/or CRC staff will collect a single blood sample of approximately 60 mL from each subject in order to measure hemoglobin A1c, glucose, c-peptide, lipid panel, high sensitive C-reactive protein (hsCRP), and TNF-α. The fasting glucose and c-peptide will be used to calculate the Homeostatic index of insulin resistance (HOMA-IR).

The blood draw for hemoglobin A1c will be in a lavender top tube (whole blood sample). The hemoglobin A1c assay must be run immediately by the Hershey Clinical Lab, however subjects will not be excluded based on their baseline lab hemoglobin A1c. A lab hemoglobin A1c result obtained from the Hershey Clinical Lab within 2 weeks before the baseline visit can be accepted as the baseline lab hemoglobin A1c, otherwise a lab hemoglobin A1c from the Hershey Clinical Lab will be obtained at in-person baseline study visits.

The samples for glucose, lipid panel and hsCRP will also be run immediately. Blood samples for c-peptide and TNF-α will be frozen at -80^{o}C. The c-peptide samples will be collected in a green top with heparinized plasma and stored to be analyzed later under this protocol. The TNF-α samples will be stored to be analyzed later, but they will not be analyzed under this protocol. Validated assays with intra- and inter-assay coefficients of variation less than 15% will be used.

Within 5 minutes of having their blood drawn, subjects will be asked to check their glucose level via finger stick on their glucometer (optional), and via their continuous glucose monitor (if they have one). Research staff will compare glucose readings from the different sources to assess accuracy and calibration of subjects' devices. The research staff will notify subjects of discrepancies once lab reference glucose results are obtained, and advise subjects to refer to the Glucometer Best Practices and Blood Glucose Meter Correlation handout they were given at their baseline visit. Accuracy of glucometer will be defined as within 15% of lab reference value if $\geq$ 100 mg/dL, or within 15 mg/dl of lab reference value if < 100 mg/dL (Klonoff et al., 2018). This is recommended when reporting glucose data in clinical research (Schnell et al., 2015). Glucometer brand and sub brand, test strip brand, and other important information regarding how subjects are using their diabetes devices will also be collected.

All of these laboratory assessments will be obtained at the baseline visit, 2-month visit and 6-month visit. If a study visit is conducted remotely, or if a subject misses a study visit, the research coordinator will obtain and record any available outside lab results, including hemoglobin A1c, glucose, and Lipid panel.

Home A1cNow Self Check Kit (in-person and remote study visits):

All subjects will be asked to perform a home hemoglobin A1c test using the Home A1cNow Self Check Kit at baseline, 2-month, and 6-month (in-person or remote) study visits. A screening Home A1cNow Self Check Kit hemoglobin A1c result within 2 weeks before the

baseline visit can be accepted as the baseline home hemoglobin A1c, otherwise a Home A1cNow Self Check Kit hemoglobin A1c will be collected at the baseline visit. Subjects will not be excluded based on their baseline home hemoglobin A1c.

Salivary collection procedure (in-person study visits): Saliva will be collected for cortisol and α-amylase at the baseline study visit (and also at the 2-month and 6-month study visits). At each study visit, the research coordinator will collect 2 saliva samples: 1) Just before the study visit starts, and 2) immediately after the study visit ends. Given the diurnal variation of salivary cortisol and α-amylase, it will be important that time-of-day of the study visits is consistent within each subject, although this will not always be feasible to implement due to scheduling logistics. Saliva will not be collected from subjects if study visits are conducted remotely.

Subjects will be instructed not to eat or drink (except for water), chew gum, smoke, brush their teeth, exercise physically, or consume prescription or over-the-counter medications 60 minutes prior to sample collection. The research coordinator will follow the written step-by-step Salivary Cortisol Collection Instructions to collect whole saliva samples from the subjects using the gold standard passive drool method. The saliva collecting equipment (Salimetrics, State College, PA) will consist of a saliva collection aid (SCA) and cryovials. Cryovials will be pre-labeled with the subject number, study visit (baseline, 2-month, and 6-month) and sample number (S1, S2) using freeze resistant labels. When collecting a saliva sample, the research coordinator will instruct the subjects to allow saliva to pool in their mouth. Then with their head tilted forward, gently guide the saliva through the SCA into the cryovial, and fill it to the required volume. The samples will be stored in secured -80^{o}C freezers at the Penn State Institute for Personalized Medicine. The saliva samples will be stored to be analyzed later for cortisol, α-amylase and other parameters, but they will not be analyzed under this protocol.

The research coordinator will complete the Saliva Cortisol Collection Questionnaire in REDCap, recording the date and time when each sample was taken, and subjects' responses to questions about consumption of food or drink, alcohol, caffeine, gum, and prescription and over-the-counter medications, brushing their teeth, exercise activities, dental work, and problems with their gums, teeth or mouth around the time of each sampling. The research coordinator will also complete the Steroid Medication Questionnaire (included in the Visit Questionnaire) and record any steroid medications subjects are currently taking including steroid skin creams, ointments and injections.

Hair and nail samples (optional protocol procedures for in-person study visits) will be collected by the research coordinator at the baseline study visit (and also at the 2-month and 6-month study visits). Hair and nail samples will be stored to be analyzed later for cortisol and other hormonal and metabolic parameters, but they will not be analyzed under this protocol. Hair and nail samples will not be collected from subjects if study visits are conducted remotely.

Subjects who consent to collection of hair and nail samples will respond to questions about their hair and nail care as part of the self-administered Participant Questionnaire in REDCap, including questions about their hair washing, use of hair products, swimming in a chlorine pool, whether they typically exercise 2 or more hours per day, habitual nail-biting, use of nail polish or other fingernail treatments, etc.

There are several reasons for measuring cortisol in saliva, hair and nail samples. Saliva cortisol is a physiological measure of acute stress, whereas hair and nail cortisol are more integrated physiological measures of hypothalamic-pituitary-adrenocortical (HPA) activity and thus reflect chronic stress exposure (Meyer et al., 2014; Hodes et al., 2017). The stress hormone cortisol is gradually incorporated into the growing hair shaft. As human scalp hair grows on average 1 centimeter per month, cortisol levels obtained from hair segments several centimeters in length is a validated biomarker of stress experienced over a few months. A second reason to measure hair cortisol in our study is that hair cortisol has been linked with obesity, which is a common comorbidity of diabetes (Jackson et al., 2017). Finally, a preliminary

study suggests that mindfulness training may decrease hair cortisol levels in smokers (Goldberg et al., 2014).

Assessment of cortisol levels in nail samples is another potential biomarker of chronic stress. The importance of also measuring cortisol in nail samples is that it represents a different timeline of hormone incorporation than scalp hair, and it can be obtained from subjects who lack scalp hair or from subjects in whom scalp hair is not available for other reasons (Doan et al., 2018).

Leftover blood, saliva, hair and nail samples: If subjects agree, their leftover blood, saliva, hair and nail samples will be stored and used for future research studies. These future studies may provide additional information about the biological factors associated with variability in the response to MBSR in patients with diabetes, which could increase our understanding of the mechanisms underlying the variability and also inform the development of more personalized mindfulness-based interventions for diabetes. Dr. Raja-Khan will determine how the samples may be used or shared. The leftover samples will be labeled with a code number only and stored in secured -80^{o}C freezers in the Penn State Institute for Personalized Medicine. Subjects who change their mind about the storage of their leftover samples will contact Dr. Raja-Khan in writing in order to withdraw their permission. If they withdraw their permission, the samples will be destroyed.

Baseline Physical Exam:

A brief physical exam will be performed on all subjects who have an in-person study visit at the CRC with the collection of the following measures by the research coordinator while subjects are dressed in light clothing without socks or shoes:

- Height recorded to the nearest 0.1 cm
- A Tanita scale will be used to record weight to the nearest 0.1 kg, body mass index (BMI) in kg/m^2, and body composition (Percent Body Fat, Fat Mass, Fat Free Mass, Basal Metabolic Rate, etc.) using advanced bioelectric impedance analysis technology (Ritchie et al., 2005). A data validation check will be performed in REDCap verifying that the BMI recorded from the Tanita scale is valid compared with the BMI calculated by REDCap from the subject's recorded weight and height. If the subject has an electronic medical implant such as a pacemaker, the Tanita scale will not be used because the electrical signal traveling through the body may interfere with the operation of an electronic medical implant. In this scenario, or if a printout from the Tanita scale cannot be obtained, a regular scale will be used to record the subject's weight in kg, and the BMI will be calculated in REDCap. The Tanita scale can be safely used during pregnancy, but it will not give an accurate reading.
- Waist and hip circumferences will be recorded to the nearest 1 cm. Waist will be measured at the level of the umbilicus and hip circumference will be measured at the widest diameter. Waist to hip ratio (WHR) will be calculated in REDCap.
- Blood pressure will be determined in the right arm after resting in a seated position for at least 5 minutes. A large cuff will be used when necessary. Three separate systolic and diastolic blood pressure measurements will be obtained and recorded at least 1 minute apart and averaged in accordance with American Heart Association (AHA) recommendations (Pickering et al., 2005). Mean arterial pressure (MAP) will be calculated as 2/3 mean diastolic blood pressure + 1/3 mean systolic blood pressure. Pulse will also be recorded.

(This physical exam will be repeated at the 2-month visit and 6-month visit). If the visit is conducted remotely, these measures will be collected from medical records and/or from subjects' self-report.

Medications:

Subjects will be asked to bring their current medication list to the remote or in-person baseline study visit (as well as to the subsequent 2-month and 6-month study visits). The research coordinator will record the names and doses of all current medications and supplements and whether medications or supplements were changed, started, or stopped during the study. If the participant does not bring their current medication list, their current medications will be obtained from their medical records.

Baseline Questionnaires:

The Baseline Medical History questionnaire will be given or mailed to subjects at the screening visit to be completed at home since many of the questions about hospitalizations and family history may need to be researched by the subject for accuracy. Subjects will complete the Baseline Medical History questionnaire electronically or on paper. If they complete a paper form, they will be asked to mail it back. They can also bring the paper form to their baseline visit if it is being done in the CRC. The Baseline Medical History questionnaire will ask about the presence of diabetes complications and co-morbidities (retinopathy, neuropathy, nephropathy, high blood pressure, high cholesterol, heart attack, stroke, etc.), as well as about any hospitalizations or ER visits over the past 2 years. The following will also be collected at baseline: Type of diabetes, Number of years with diagnosed diabetes, Insulin treated vs. non-insulin treated, Marital status, Work status, Education, and Income. The research coordinator will review the Baseline Medical History questionnaire for completeness. If any answers are missing, the research coordinator will ask the subject: "Are you sure you meant to skip this question?" If the subject did not mean to skip the question, the research coordinator will record the subject's response.

Medical records will be reviewed at baseline (and throughout the study) to confirm reasons for any hospitalizations and/or ER visits whenever applicable, as well as to confirm any new major diagnoses subjects report during the study. Adverse Event Reports will be completed when indicated.

At the baseline visit, all subjects will complete the Orientation Questionnaire, which will be available to the MBSR and SME instructors in REDCap as they need this information for Orientation purposes.

The Behavioral Risk Factor Surveillance System (BRFSS) Adverse Childhood Experience (ACE) and the Childhood Trauma Questionnaire (CTQ) will be assessed at baseline only (Felitti et al, 1998; Dube et al, 2001; Bynum et al., 2009; WHO, 2018; CDC, 2020a; CDC, 2020b). ACEs are a risk factor for chronic disease, and there is preliminary evidence that people with more ACEs benefit more from mindfulness (Williams et al., 2014; Korotana et al., 2016). Four ACE scores will be calculated:

1- BRFSS ACE score of 0 to 8 will be calculated using the 11 questions that are in the Centers for Disease Control and Prevention (CDC) Behavioral Risk Factor Surveillance System (BRFSS) ACE module.

2- Modified BRFSS ACE score of 0 to 8 will be calculated. This includes one additional question from the World Health Organization Adverse Childhood Experiences International Questionnaire (WHO ACE-IQ) about parental death which is incorporated into the parental separation or divorce category.

3- CDC-Kaiser ACE score of 0 to 10 will be calculated as in the CDC-Kaiser ACE Study using the 11 questions that are in the BRFSS ACE module, 5 questions from the Childhood Trauma Questionnaire (CTQ) for an emotional neglect ACE, and 5 questions from the CTQ for a physical neglect ACE. This includes the parental divorce or separation question, but does not include the parental death question.

4- Modified CDC-Kaiser ACE score of 0 to 10 will be calculated. This includes one additional question about parental death which is incorporated into the parental separation or divorce category.

The BRFSS ACE and CTQ questionnaires are self-administered under the guidance of our study psychologist Dr. Dahlia Mukherjee. As is recommended, we preface these questionnaires by informing subjects beforehand that some of the questions may make them feel uncomfortable, and they are free to skip any of the questions they do not want to answer.

If the study visit is conducted remotely, the subject will be e-mailed a link from REDCap to complete the self-administered questionnaires during the (PSH Teams) live videoconferencing study visits.

<u>The following questionnaires will be self-administered at the baseline study visit (and also at the 2-month and 6-month study visits), starting with the Toronto Mindfulness Scale after sitting quietly for 15 minutes:</u>

The Toronto Mindfulness Scale (TMS) will assess mindfulness (Lau et al., 2006). Prior to completing the TMS questionnaire, subjects will be instructed to ‘‘sit quietly for the next 15 minutes and pay attention to your breathing or anything else that might arise.’’ Afterwards, subjects will be asked to describe the degree to which each of the 13 items in the TMS described what they just experienced on a 5-point scale from 0 (not at all) to 4 (very much). The TMS measures an individual’s ability to generate mindfulness, a mode of curious, decentered awareness dependent on the development of a composite set of skills.

The Acupuncture Expectancy Scale will be modified to a Stress Reduction Expectancy Scale (SRES) and used to assess subjects’ expectations at baseline and at subsequent study visits (Mao et al., 2007; Mao et al., 2010; Bauml et al., 2014).

The 15-item Food Craving Questionnaire-Trait-Reduced (FCQ-TR) will be assessed as it has been shown to be responsive to a mindfulness-based intervention (Mason et al., 2017; Meule et al., 2014; Epel et al., 2014).

The 3-item Walking Enjoyment scale, an abbreviated version of the Physical Activity Enjoyment Scale (PACES), will be used to assess different aspects of walking enjoyment (e.g., ‘‘I enjoy doing brisk walking.’’) on a one- to five-point scale. Higher scores indicate greater enjoyment. The original PACES has adequate test-retest reliability (r =. 77) and good construct validity (Kendzierski & DeCarlo, 1991). The abbreviated version also has some validity though it is less than the original PACES. The abbreviated version is preferable for this study because it is shorter.

The 17-item Diabetes Distress Scale (DDS) will assess diabetes-related distress (Polonsky et al., 2005).

The Perceived Stress Scale-10 (PSS-10) will assess subjective stress (Cohen & Williamson, 1988). The PSS-10 has been linked with adverse health outcomes and poor dietary and physical activity behaviors (Arnold et al., 2012; Barrington et al., 2012). Our pilot data shows PSS-10 significantly improves with MBSR (Raja-Khan et al., 2017).

The Short Form-12 (SF-12), a validated shorter version of the SF-36, will assess health related quality of life (Ware et al., 1996).

The Positive and Negative Affect Schedule (PANAS) will assess psychological affect (Watson et al., 1988).The Generalized Anxiety Disorder scale (GAD)-7 will also be self-administered (Spitzer et al., 2006).

The PROMIS Short Form v1.0 Sleep Disturbance 8a will be self-administered. The PROMIS-Sleep Disturbance items assess self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep. This includes perceived difficulties and concerns with getting to sleep or staying asleep, as well as perceptions of the adequacy of, and satisfaction with, sleep. The PROMIS-Sleep Disturbance has demonstrated excellent validity as evidenced in

associations with disease activity, depression, female sex, smoking, and use of corticosteroids or narcotics (N=3173; inflammatory bowel disease) (Ananthakrishnan, 2013), ability to distinguish among those with and without sleep disorders (Buysse, 2010), and prediction (along with negative affect) of global ratings of improvement in back pain (Karp, 2014). The HealthMeasures Scoring Service, powered by Assessment Center℠, will be used to score the PROMIS Short Form v1.0 Sleep Disturbance 8a. The HealthMeasures Scoring Service is a free, web-based application that scores an Excel file of raw participant responses and returns by email a file with calculated T-scores for all measures. Further details are available at: http://www.healthmeasures.net/index.php?option=com_content&view=category&layout=blog&id=190&Itemid=1214

The Patient Health Questionnaire-9 (PHQ-9) will assess safety at each study visit (Kroenke et al., 2001; Van Steenbergen-Weijenburg et al., 2010). This will be self-administered at the study visits as described above in the screening visit. As in the screening visit, if a subject scores 1 or greater on the 9th item of PHQ-9, the research coordinator will interview the subject using the modified P4 Screener to assess suicide risk (Dube et al., 2010).

The Modified Coronavirus Impact Scale will be self-administered to assess how much the Coronavirus pandemic has impacted different aspects of subjects' lives. This survey was modified from the Coronavirus Impact Scale created by Stoddard and Kaufman (https://www.nlm.nih.gov/dr2/Coronavirus_Impact_Scale.pdf).

Subjects will respond to additional questions in a Participant Questionnaire at the baseline visit (and subsequent study visits). This Participant Questionnaire will assess:

- Adherence to Diabetes Medications by asking subjects to "Rate your ability to take all your diabetes medications as prescribed over the past month'' (with six choices: Very poor, poor, fair, good, very good, and excellent) based on a previous study that determined that such a self-report measure most accurately assessed HIV medication adherence (Lu et al., 2008).
- Follow-up Medical History by asking subjects if there have been any changes to their health since the last visit.
- Number of sick days in the past 4 weeks
- Questions about current employment status
- A question about burnout
- Questions about current use of tobacco and alcohol
- Hair and nail care if they agreed to provide hair and nail samples
- And other questions

The Counterfactual Measurement questionnaire will be self-administered at the baseline study visit (as well as at the 6-month study visit) to capture cross-contamination of behaviors throughout the study (e.g. active SME control subjects electing to participate in mindfulness activities). The Counterfactual Measurement questionnaire will ask subjects about the frequency and duration of engagement in mindfulness activities, other meditative activities, and other relevant activities over the past 6 months, both outside of the study and as a part of the study. Subjects' responses at the subsequent study visits could reveal group assignment, thus the research coordinators will be blinded to the subjects' responses to this instrument in REDCap.

The Stress Experience Survey will be administered by the research coordinator at the baseline study visit (and also at the follow-up phone call after Class #4, the 2-month study visit, and the 6-month study visit). This includes questions about the 10 most common meditation-related symptoms (items 1 to 10), as well as a question about other stress-related symptoms. This survey was adapted from Dr. Willoughby Britton's MBP-Specific Adverse Effects Survey (Britton_Version9.18.19), which represents the 10 most common meditation-related symptoms

from the Varieties of Contemplative Experience Phenomenology Codebook (Lindahl et al., 2017), as replicated in an NIH-funded mindfulness-based intervention clinical trial (Britton, in prep).

The Hypoglycemia Survey will be administered by the research coordinator at the baseline study visit (and also at the follow-up phone call after Class #4, the 2-month study visit and the 6-month study visit). The research coordinator will ask subjects about self-reports of Level 2 hypoglycemia (glucose < 54 mg/dL) and Level 3 hypoglycemia (hypoglycemia requiring the assistance of another person for treatment). Level 2 hypoglycemia will be recorded as an Adverse Event. Level 3 hypoglycemia will be recorded as a Serious Adverse Event (See DSMP).

Subjects will complete the Phone Call Time Preference questionnaire at the baseline study visit and at the 2-month study visit, as they did at screening, indicating their preferred windows of time to receive phone calls for visits and scheduling appointments. Subjects will be instructed that 3-hour windows of time are preferable (e.g. 6-9 PM on Wednesdays is better as it allows for more flexibility than 8-9AM, 1-2PM, and 5-6PM).

Data from subjects' diabetes devices (glucometers, continuous glucose monitor (CGM), insulin pump and other smart insulin delivery devices) will be collected at each remote or in-person study visit:

Description of the concept: Standards of medical care in diabetes include the use of glucometers by patients to self-monitor their blood glucose (SMBG) levels to achieve glycemic targets. In recent years, commercially-available continuous glucose monitors (CGMs), which measure interstitial glucose levels every few minutes for 24 hours a day, are increasingly being used by patients to monitor their glucose levels. In standard clinical practice, computer software are used to collect data from subjects' diabetes devices (glucometers, CGMs, insulin pumps and other smart insulin delivery devices) in order to assess their glycemic control and determine changes in treatment.

Description of the procedure: Subjects will be asked to bring their diabetes devices (glucometers, CGM, insulin pump and other smart insulin delivery devices) to each remote or in-person study visit. At the screening visit, and at each subsequent study visit, the research coordinator will ensure that the date and time are correct on the subjects' diabetes devices. The research coordinator will record the date and time that are on each device. If the date or time on a device are not correct, the research coordinator will record the device date and time offset, and work with the subject to correct the date and time on the device. Correcting the date and time on the device does not correct the date and time of the data that has already been collected.

The research coordinator will obtain and record any available diabetes device data or reports that are provided by the subject or obtained from remote study Clarity/LibreView accounts, or clinic diabetes device accounts and medical records. This data will be manually recorded. The coordinator will collect reports of aggregated and raw data from these diabetes devices at the baseline, 2-month, and 6-month study visit time points. Aggregate reports will be collected for 14-days (which is the American Diabetes Association recommended standard for aggregating CGM data), 30-days, 60-days, and 90-days with an end date of the day before the study visit. All available reports will be collected e.g. Dashboard, Blood Glucose Trends-Hourly, Therapy Timeline, CGM Hourly, Logbook, etc. Strategies that may be used to collect this data include:

- The subject will be asked to share data reports from their devices with the research team.
- The research coordinator will use computer software to collect the data from these devices at the study visits.

- The research coordinator will use a secure cloud based diabetes-management system (e.g. Clarity, LibreView) to collect the subject's data anonymously using their study ID number instead of their name or other identifying information. When applicable, subjects will be invited to upload or connect their diabetes devices to deidentified patient profiles in the study Clarity and LibreView accounts.
- The research coordinator will look through the data in a subject's glucometer and record it e.g. In the case of a glucometer the research coordinator will record the following Summary screen data: % In-Range, Checks/Day, Highest glucose, Average glucose, and Lowest glucose in the past 14-days, 30-days, 60-days, and 90-days.
- If the subject is a patient in the Endocrinology clinic, the coordinator will also have access to their diabetes device data in the Endocrinology clinic Glooko, Clarity and LibreView accounts.
- Diabetes device reports in the subject's medical records.

Reports that are collected from devices-- will be saved in a secure location. Data will be abstracted from these reports. When available, data will be abstracted from the Ambulatory Glucose Profile (AGP) which is a standardized, single page report that includes glucose summary statistics. The AGP offers a report that is consistent regardless of device.

During the study, if a subject is not using a CGM, they will be advised to use their own glucometer and testing supplies to check their blood glucose at least four times per day, including:

- Fasting (before breakfast or the first meal of the day)
- Before lunch
- Before dinner
- Before bed
- When having symptoms

This is in-line with general recommendations for patients with uncontrolled diabetes, or patients on multiple daily injections of insulin or an insulin pump. If a subject is testing fewer than 4 times a day, they will be advised to alternate their testing times e.g. check fasting and before lunch on some days, fasting and before evening meal on other days, and fasting and before bed on other days.

The research coordinator will encourage subjects to bring their glucometers to each remote or in-person study visit even if they are not checking their blood sugars as prescribed. The research coordinator will encourage subjects to bring their CGM, insulin pump and other smart insulin delivery devices to each remote or in-person study visit even if they have not been using them every day.

How/if devices need to be provided to subjects: Subjects will use their own glucometers, CGMs, and insulin pumps and other smart insulin delivery devices. At the screening, baseline and 2-month study visits, subjects who do not have a working glucometer but report using a glucometer before, will be offered a sample glucometer kit (if available), and advised to check with their insurance regarding coverage of additional glucometer testing supplies (e.g. test strips and lancets), and to see their PCP for prescriptions for additional glucometer testing supplies. The research coordinator will work with the subject to ensure that the correct date and time are set on the sample glucometer they are given. Subjects will be asked to bring their sample glucometer to their subsequent remote or in-person study visits so that data can be collected from them. Subjects paying out of pocket for glucometer testing supplies will be advised to consider Walmart's ReliOn brand testing supplies which are more affordable. Subjects who have

never used a glucometer will be advised to see their PCP for a glucometer and referral to a Diabetes Educator.

Who will be managing this data: The research coordinator will be managing this data.

When will this data be collected throughout the trial: We will collect this data from subjects' diabetes devices (glucometers, CGMs, insulin pumps and other smart insulin delivery devices) at their remote or in-person baseline, 2-month, and 6-month study visits.

What important pieces of data are being collected from this procedure throughout the trial:

Glucometer Data to be collected include:

- Glucometer download start and end dates
- Average blood glucose level from glucometer (mg/dL) overall and during specific times of the day (Morning, Afternoon, Evening, and Night time windows)
- Standard deviation of all blood glucose readings from glucometer (mg/dL)
- Number of blood glucose readings per day on average (Readings/Day)
- Total number of blood glucose readings (# Readings)
- Percent of blood glucose readings Above target (frequency of hyperglycemia)
- Percent of blood glucose readings In Range
- Percent of blood glucose readings Below target (frequency of hypoglycemia)
- Lower limit of overall target from glucometer (mg/dL)
- Upper limit of overall target from glucometer (mg/dL)
- Lowest blood glucose reading (mg/dL)
- Highest blood glucose reading (mg/dL)
- Device information, e.g.

Glucometer #1: Name of Device, Device time offset (hh:mm), and Last sync date
Glucometer #2 Name of Device, Device time offset (hh:mm), and Last sync date

Additionally, from the above glucometer data, we will be able to determine the Coefficient of Variation (CV), which is a measure of glucose variability calculated as the standard deviation divided by the mean glucose. The CV has been proposed as the preferred measure of glucose variability (Suh & Kim, 2015; DeVries, 2013; Rodbard, 2011). Glucose variability is a challenge for many patients with diabetes as it increases one's risk for hypoglycemia and has been linked with increased cardiovascular risk in some studies (Jun et. al., 2015).

CGM Data to be collected include:

- Name and Model of CGM device
- CGM download start and end dates
- Number of days included in the download
- Average glucose level overall from CGM (mg/dL)
- Average glucose level every hour from CGM (e.g. midnight to 1AM, 1AM to 2AM, 2AM to 3AM, etc.)
- Percent of glucose readings Very Low (< 54 mg/dL) as the frequency of severe hypoglycemia from CGM
- Percent of glucose readings Low (< 70 mg/dL) or below target as the frequency of all hypoglycemia from CGM
- Percent of glucose readings In Target Range (70 – 180 mg/dL) from CGM
- Percent of glucose readings High (> 180 mg/dL) or above target as the frequency of all hyperglycemia from CGM
- Percent of glucose readings Very High (> 250 mg/dL) as the frequency of severe hyperglycemia from CGM

- Coefficient of Variation (%) as a measure of glucose variability from CGM
- Standard deviation of glucose (mg/dL) as another measure of glucose variability from CGM
- Lower limit of overall target from CGM (mg/dL)
- Upper limit of overall target from CGM (mg/dL)
- Percent of Time CGM Active for Dexcom CGM users

Collected measures will include the standardized CGM metrics for clinical care recommended by the American Diabetes Association and the International Consensus on Time in Range for CGM (American Diabetes Association 2019b; Battelino et al., 2019):
1- Number of days CGM worn (recommend 14 days)
2- Percentage of time CGM is active (recommend 70% of data from 14 days)
3- Mean glucose
4- Glucose management indicator (GMI)
5- Glycemic variability (% Coefficient of variation) target ≤ 36%
6- Time above range (TAR): % of readings and time in hyperglycemic range, i.e., >250 mg/dL (level 2), 181-250 mg/dL (level 1)
7- Time in range (TIR) % of readings and time in target range, i.e., 70-180 mg/dL
8- Time below range (TBR) % of readings and time in hypoglycemic ranges, i.e., <54 mg/dL (level 2), 54-69 mg/dL (level 1)

Insulin pump data to be collected include:

- Name of insulin pump
- Name of insulin used in insulin pump
- Aggregate Number of Days
- Average Daily Carbs (grams/day)
- Standard deviation of daily carbs (grams/day)
- Carbs/Bolus Insulin (grams/Units)
- Average Total Daily Dose of Insulin (units of insulin per day)
- Standard deviation of number of units of insulin per day
- Average Daily Basal Insulin (units/day)
- Percent Basal Insulin
- Average Daily Bolus Insulin (units/day)
- Percent Bolus Insulin
- Average Number of boluses per day

For those subjects with a Medtronic Insulin pump Hypoglycemic and Hyperglycemic Patterns will also be collected

Accelerometer data will be collected using the Actigraph wGT3X-BT activity monitor to objectively measure physical activity (optional protocol procedures):

Description of the optional Actigraph wGT3X-BT device and how it should be worn and for how often: The Actigraph wGT3X-BT activity monitor is a small, unobtrusive tri-axial accelerometer (an activity monitor that is similar in size and function to a pedometer, but more accurate than a pedometer). Compared to four other commonly used accelerometers, the Actigraph was found to have the least variability and the highest overall reliability with G values above .60 and ICC values above .80 (Welk et al., 2004; Sasaki et al., 2011).

If a subject opts in to wearing an Actigraph and collecting the accelerometer data, they will be instructed to wear the Actigraph for at least 12 hours a day over at least 7 days around each of 3 study visit time points (baseline, 2-month, and 6-month). The time windows for capturing the optional Actigraph data are +/- 2 weeks of the baseline and 2-month study visits, and in the 4 weeks before the final 6 month study visit. Subjects will be provided with a

waistband/belt and instructed to wear the Actigraph on the waistband/belt over their hipbone, in line with their knee. They will also be asked to keep a written daily log of their Actigraph wear time, including when they put on/took off the Actigraph to enable additional confirmation of the Actigraph activity data. Subjects will be instructed to put the Actigraph on first thing in the morning when they wake up and record the time on their log, and to take it off at night just before getting into bed and record the time on their log. Subjects will be instructed not to wear the Actigraph when sleeping, showering or swimming, and to note on the log if they briefly removed the Actigraph.

The research coordinator will ensure that subjects understand how to accurately wear the Actigraph, and provide them with written instructions on how to wear the Actigraph.

How the optional Actigraph devices will be provided to the subjects: The research coordinator will either (1) Provide the Actigraph to the subject at their study visit along with instructions on how to wear the device and a postage paid envelope to mail the device and Actigraph Wear Time Log back after they have worn it for 7 days, or (2) Mail the Actigraph to the subject with instructions on how to wear the device. The preferred method for in person visits will be to provide the Actigraph to the subject at their baseline and 2-month visit, and mail the Actigraph to the subject before their final 6-month study visit. When subjects will be given the Actigraph at an in-person study visit, the subject's weight from the in-person visit will be used to initialize the Actigraph. When subjects will be mailed the Actigraph, their weight from their medical records if within the study visit time window will be used, and if that is not available then their weight from their last study visit will be used, and if that is not available then a self-reported weight will be used. If the baseline and 2-month visits are conducted remotely, the Actigraphs will be mailed to the subject. For remote and in-person study visits, the Actigraph will be set to start recording at midnight and subjects will be instructed to start wearing the Actigraph the morning after they receive it.

The research coordinator will call the subject if the Actigraph was not returned within 14 days after they were scheduled to start wearing it.

The research coordinator will follow the recommended steps to test, initialize and fully charge the Actigraph prior to each use. Each new Actigraph device will be worn and tested by the research team, and the test data will be reviewed briefly by the research team. Actigraph devices will be sanitized and waistbands laundered in between use. Actigraphs will be labeled with who to call and where to return the device if lost and found.

Who will be managing and aggregating this data: The research coordinators will initialize the devices, and upload the (optional) collected Actigraph data into the ActiLife software platform. Biometric data (height, weight, date of birth, dominant side, etc.) is entered at the time the devices are initialized and prepared for distribution for data capture. The most current updated weight measurement available to the research coordinator will be used to initialize the device (whether that be measured at an in-person study visit, extracted from the medical records, or self-reported by the participant, when necessary). This information is important to obtain accurate metabolic equivalents (METs) calculations in the software algorithms/formulas (because a change of a few kilograms will have an effect on the energy expenditure and METs calculations). When applicable/necessary, it is possible that the biometric data may also be entered/updated at the time of scoring at the end of the study. The research coordinators will work with the data manager/statistician to reconcile any data entry or quality issues. *Refer to the Actigraph Device Data Monitoring SOP for more detailed information and procedures.* As the processing and wear-time validation of accelerometer data is a developing and evolving field, the wear-time validation algorithm and criteria will be decided for analysis at the end of the study, when more current literature can be reviewed. If possible, ideally the wear period will meet either the initial Sallis validation criteria of at least 5 valid days containing at least 10 valid hours per day, or the alternate Sallis validation criteria of at least 66 valid hours (Cain &

Geremia, 2012). At the end of the study, once the wear-time validation algorithm and processing criteria are decided upon after review of more current literature at that time, the Actigraph data will then be processed and scored for analysis, likely using Freedson VM3 2011 for Energy Expenditure Scoring and Cut Points/MVPA Scoring (Sasaki et al., 2011), and Freedson 1998 for METs (unless Freedson VM3 2011 or updated algorithms become available options later at the time of scoring and analysis) (Freedson et al., 1998). Actigraph data will be reviewed regularly by the data manager/statistician. Kalen Kearcher, MS, ACSM EP-C, an exercise physiologist experienced in using the Actigraph, will be briefly available for consultation with the research team regarding questions in the use of the Actigraph wGT3X-BT and the ActiLife software that will be used to score the data. The research team will read the ActiLife 6 User's Manual, the User Guide for the ActiGraph wGT3X-BT + ActiLife, and Sallis's Accelerometer Data Collection and Scoring Manual For Adult & Senior Studies (Cain & Geremia, 2012).

How often will this data be collected throughout the trial: This optional data will be collected for 7 days around each of 3 study visit time points (baseline, 2-month and 6-month).

What important pieces of data are being collected from the Actigraph wGT3X-BT devices throughout the trial:

The optional Actigraph will be worn for 7 days and data will be stored as 10 second epochs (and possibly later converted to 60-second epochs). This data will be used to determine average daily:

- Step count data
- Sedentary – Length of time in minutes in Sedentary activity [<100 counts per minute (60-s epoch)]
- Light - Length of time in minutes in Light physical activity [100-1951 counts per minute (60-s epoch)]
- Moderate - Length of time in minutes in Moderate physical activity [1952-5724 counts per minute (60-s epoch)]
- Vigorous - Length of time in minutes in Vigorous physical activity [5725-9498 counts per minute (60-s epoch)]
- Very Vigorous - Length of time in minutes in Very Vigorous physical activity [≥9499 counts per minute (60-s epoch)]
- Moderate to Vigorous Physical Activity (MVPA) – Length of time in minutes in MVPA [3 metabolic equivalents (METs) or greater] (≥ 1952 counts per minute) using established activity count "cut-points" (Freedson & Miller, 2000). Total minutes of MVPA on valid days will be divided by the number of valid days to obtain the average daily minutes of MVPA.
- Other measures

Dr. Liza Rovniak, an NIH-funded exercise scientist, will provide her expertise and consultation in the assessment of these data.

24-hour Dietary Recall Surveys (optional protocol procedures):

Dietary intake data for 24-hour recalls (optional) will be collected and analyzed using the Automated Self-Administered 24-hour (ASA24) Dietary Assessment Tool, version 2020 and version 2022, developed by the National Cancer Institute, Bethesda, MD (https://epi.grants.cancer.gov/asa24). Optional modules that will be included in the ASA24 are: Location, Food Source, TV/Computer, and Nutrition Report Viewing. The amount of time provided to complete the ASA24 recall will be set to 24 hours so that it has to be completed by midnight of the prompted reporting day (and so that the intake day is always referenced as 'yesterday' when participants are prompted to complete the 24-Hr Recall). This means subjects will get an email invitation to complete the ASA24 recall in the morning and have until midnight to complete it, recording data about the foods they have eaten throughout the entire (24 hour) previous calendar day. The research coordinator will provide subjects with information about

the ASA24 self-administered dietary assessment tool, handout titled ASA24 /Quick Start Guide 24 hr recall, and the following link to the ASA24 demo as part of their introduction/training https://asa24.nci.nih.gov/demo/. The research coordinator will send subjects 2 unannounced emails inviting them to complete 1 weekend and 1 weekday diet recall (optional) on the ASA24 website during the following time windows: within 2 weeks before Class #1, 2 weeks after Class #8, and 2 weeks before Booster #4 (Miller et al., 2009). These emails will include the link to the ASA24 website, and the username and password the participant will need to enter to complete a recall. Participants will need to be connected to the internet to complete a recall. The research coordinator will visit the ASA24 Researcher Website to view participants' data, and monitor the number of completed intakes per participant. If a subject does not complete a diet recall, the research coordinator will contact the subject and remind them to check their email every day, and then send another unannounced email inviting the subject to complete the diet recall.

All food intake (24-hour recall) data, data about the foods they have eaten on the previous day, will be collected via the ASA24 self-administered dietary recall. The types of questions that are asked depend on the foods they have eaten. See attached sample ASA24 overview 2020, and ASA24 - 2020 researcher instructions.

Data Storage, Security and Transmission: Researchers using the ASA24 system do not provide the NCI, Westat, or the ASA24 system with any identifying data for participants of their studies. Rather, researchers specify a unique numeric identifier for each respondent and download system-generated usernames and encrypted passwords that they provide to respondents so that they may access the application.

The ASA24 system also does not collect any identifying data directly from respondents. However, IP address information is accessed for the purpose of routing information between the server and the respondent's computer—often the IP address is that of the user's Internet Service Provider (ISP). IP addresses are not stored or tracked by the ASA24 system. However, logs of connections are kept in the hosting environment for audit trail purposes. This information is not mined in any way but would be available if there were a legal obligation to release it.

Response data are secured at the hosting site using industry standard security controls, including firewalls and encryption. All data entered into the ASA24 system at the respondent's computer is encrypted by the internet browser (e.g., Internet Explorer, Firefox) before they are transmitted to our servers using Secure Socket Layer (SSL) Technology. SSL allows for the authentication of the sending and receiving computers.

Only a particular study's investigator(s) and the ASA24 operations team can access response data. Access is gained through usernames and strong passwords. Data are maintained in the ASA24 system for a period of at least one year (unless the Researcher requests an earlier date for data purging). Researchers will be notified before their data are removed from the system.

Who will be analyzing this data: This data will be analyzed by the study biostatistician.

When will this data be collected throughout the trial: 24-hour dietary recall data (optional) will be collected on 1 weekend and 1 weekday within 2 weeks before Class #1, 2 weeks after Class #8, and 2 weeks before Booster #4.

How often will this data be collected throughout the trial: Two 24-hour dietary recalls (optional) will be collected on each subject around each of 3 study visit time points (baseline, 2-months, and 6-months) so each subject will have a maximum of six 24-hour dietary recalls.

What important pieces of data are being collected from this procedure throughout the trial:

-total energy intake
-carbohydrate intake
-fat intake

-protein intake

-Healthy Eating Index

There are many more variables that are generated automatically from the intake data so final data sets will contain more variables. Additional variables of interest include glycemic index, glycemic load, fiber, added sugars, fruits, vegetables etc.

These variables will be collected as the total for each 24-hour recall period.

Experience Sampling: Daily Stress & Cravings and Daily Diary Surveys

We will use experience sampling to collect daily repeated measures of participant stress levels, food cravings, and use of stress-management strategies in naturalistic contexts. Experience sampling is designed to overcome the limitations of retrospective self-report and recall bias by collecting brief, but frequent repeated reports of participant emotions, experience, and behavior. Experience sampling surveys will be administered on a daily basis to all subjects between the baseline study visit and the final 6-month study visit (or the time they are deemed lost-to-follow up or are withdrawn from the study). These surveys were initially administered four times a day via Qualtrics for the first few study cohorts. They are now being administered once a day via REDCap.

REDCap Daily Stress & Cravings Survey and Daily Diary Survey. All participants eligible to be randomized after completion of their Baseline visit will receive one email invitation per day asking them to complete the Daily Stress & Cravings Survey questions. There will be 3-4 Daily Stress & Cravings Survey questions which will take approximately 15-20 seconds to complete. Each survey will inquire about participant experiences "between 8 PM last night and 8 PM tonight."

Between Class #1 (or #2) and the final 6-month study visit (or the time they are deemed lost-to-follow up or are withdrawn from the study), the daily email invitation participants receive will ask them to complete both the Daily Stress & Cravings Survey questions and the Daily Diary Survey questions. The Daily Diary Survey questions will ask participants about the stress management activities they engaged in "between 8 PM last night and 8 PM tonight", and the amount of time spent engaged in each activity. Participants will only be asked about activities relevant to the specific condition the participant is assigned to. Participants assigned to the treatment (MBSR) condition will complete 10 questions, which takes between 10-50 seconds to complete. Participants assigned to the comparison (SME) condition will complete 2 questions, which takes between 5-10 seconds to complete.

Data Security

Unblinded research team members e.g. the SME instructors will have access to the randomization list in REDCap so that they will be able to check and make sure that subjects are completing the correct Daily Diary Survey questions that correspond to their group assignment, MBSR or SME.

During the study, subjects will be compensated an additional $15 if they respond to at least 70% of the Experience Sampling Surveys by their 2-month study visit.

Between the baseline study visit and Class #8, unblinded research team members e.g. the SME instructors will periodically review reports of subjects' Experience Sampling Survey response rates, and if a subject's response rate for the Experience Sampling Surveys (Stress and Cravings or Daily Diary) ever falls below 70% in a week, the SME instructor or other unblinded research coordinator will call the subject to troubleshoot.

Between the 2-month study visit and the 6-month study visit, the SME instructor or other unblinded research coordinator will be making monthly phone calls to the subjects to remind them of their booster sessions and encourage retention in the study. During these monthly phone calls, the research coordinator will encourage subjects to continue to respond to as many of the Experience Sampling Surveys as they are able to as their responses are very important in helping the research team better understand how day-to-day stresses affect people living with diabetes.

Who will be managing this data: Unblinded research team members e.g. the SME instructors will be managing this data. Due to the nature of this data, specifically because the MBSR and SME groups have different Daily Diary of home practice questions and responses, which would reveal group assignments, the research team members managing this data e.g. the SME instructors will not be blinded. Blinded study team members will not have access to the Experience Sampling Surveys in REDCap.

Who will be analyzing this data: The study biostatistician will analyze this data with input from Dr. Raja-Khan. However, any data that identifies the group assignments of the subjects (e.g. Daily Diary survey questions and responses about their home practice, instructors' names, etc.) cannot be analyzed by the study biostatistician or any of the blinded study team members until the study is unblinded.

At the end of the baseline visit, if a subject is deemed fully eligible for inclusion into the study, the research coordinator will:

- Inform the subject that they will receive a Randomization phone call during the week before Orientation
- Schedule the subject for the following:
    - Follow-up phone call within 2 weeks after Class #4
    - 2-month study visit
    - 6-month study visit
- Give the subject written instructions and reminders for the following:
    - Randomization phone call in the week before Orientation
    - Follow-up phone call within 2 weeks after Class #4
    - 2-month study visit
- Give the subject a Wallet card reminding them not to say anything that would reveal their group assignment when speaking to blinded study staff on the phone or at the study visits. The card will instruct the subject to call the research coordinator if they have any questions. The contact information for the research coordinator will be included on the card.

Data Collection Procedures:

Data will be collected in a thorough and systematic manner. Only study personnel blinded to group assignment will collect outcomes. We have selected measures that are quick to administer and complete to minimize burden. All data will be managed via a single platform, REDCap, a HIPAA compliant platform designed for research studies.

Data Management:

All data for this project will be promptly entered into a computerized database. Subject identifications will be kept separate in locked files and will be destroyed when no longer needed for the project. To minimize errors, measures will be verified prior to data entry and computer verification will be employed during data entry. Data files will be backed up and archived regularly.

7.2.4 Randomization and Study Intervention

Randomization is a critical feature of a clinical trial because it prevents treatment-selection biases. Subjects will be randomized after obtaining their baseline measurements and within 1 week before the start of the study intervention (Orientation). It is anticipated that the amount

of time between randomization and the start of the study intervention (Orientation) will be no more than 1 week. There will be rolling enrollment. We will run a new cohort of MBSR and SME control classes approximately every 3 months. Subjects will only be randomized to a cohort if they indicate they are available for the intervention classes for that cohort.

Two hundred ninety (290) adults with uncontrolled diabetes will be randomized with equal allocation to one of two study groups for 6 months: (1) MBSR (n=145), or (2) SME control (n=145). Subjects will then undergo study visits again at 2 months (after Class #8/after the standard 8-week MBSR or SME program) and at 6 months (after Booster session #4/end of study), where the baseline procedures and measures will be repeated.

During the study, all subjects will continue to receive usual care from their physicians and will be advised not to change or discontinue any of their medications during the study unless directed to do so by their physician. As these subjects have uncontrolled diabetes, it is expected that they will be on medical treatment as prescribed by their physician, and they will be advised to follow-up with their physician every 3 months to ensure they are on optimal medical treatment. During the study, all subjects will be encouraged to continue their routine activities and they will be asked not to take part in any other formal stress reduction programs.

Randomization to MBSR or SME control will be performed within REDCap using a pseudo-random number generator via the PLAN procedure within SAS software, version 9.4 (SAS Institute Inc., Cary, NC). Personnel in the Department of Public Health Sciences will use the PLAN procedure within SAS software to generate a randomization list using variable-size, random permuted blocks to ensure that the number of subjects in each treatment arm is balanced after each set of B randomized subjects, where B is the block size. Using a 1:1 allocation ratio, there will be 145 subjects assigned to each study group. Randomization will be stratified by insulin vs. non-insulin treated subjects to make sure the two groups are balanced as this is a potential confounder. Personnel in the Department of Public Health Sciences will choose the block sizes without revealing it to any of the blinded investigators or study personnel who will be collecting and reviewing outcomes data. Study group data will be presented in a blinded fashion within DSMB reports.

Randomization to MBSR or SME control will be performed by the SME instructors in REDCap during the Randomization phone call as described below. Study group assignments will not be communicated to research personnel who will be collecting and reviewing outcomes data. The SME instructors will communicate the study group assignments to the subjects and the MBSR instructors. The subjects and instructors will be asked to keep the assignments concealed from the blinded investigators and study personnel. The PI, research coordinators and all study personnel involved in the collection and review of outcomes data will be blinded.

Overview of study instructors and roles

There are two types of instructors in the study: the MBSR instructors and the SME instructors. The MBSR instructors and SME instructors will have access to participants' Orientation Reports in REDCap. The MBSR instructors are expected to directly communicate to the SME instructor about participant attendance at the MBSR sessions. The SME instructors are expected to record participant attendance at the MBSR and SME sessions.

Randomization Phone Call (by the SME instructor within 1-week before Orientation):

At the end of the baseline visit, if a subject is deemed fully eligible for inclusion into the study, the research coordinator will inform the SME instructor, or other designated unblinded study team member, that the subject can be randomized during the week before Orientation. The SME instructor will disseminate the allocated randomized intervention to the subjects in their cohort, as the SME instructors are not blinded and they are not involved in the collection or analysis of study outcomes. During the Randomization phone call, the SME instructor will complete the following procedures to randomly assign the subjects in their cohort to one of two study groups (MBSR or SME) in REDCap:

- The SME instructor will call the subject in the week before the Orientation session.
  - If the SME instructor is unable to reach the subject for randomization, the SME instructor will email the subject to follow-up (See SME Instructor Email Template Randomization No Contact Made).
- The SME instructor will verify that the subject is still available for the study sessions. Subjects will be informed that they must attend the Orientation session to continue in the study. If they miss the Orientation session, and are unable to make up the Orientation before Class #2, they will not be able to continue in the study. If a subject thinks they will miss the Orientation, or if they think they will miss more than 2 classes during the first 8 weeks (including Class #1 to 8 and the Retreat), they will be encouraged to wait for another wave/cohort when they are able to make the time commitment. The SME instructor will not randomize any subjects who cannot commit, with reasonable certainty, to completing an Orientation session before Class #2, and at least 7 out of 9 classes during the first 8 weeks (including Class #1 to 8 and the Retreat).
- Upon confirming the subject's commitment to attendance and interest in participation, the SME instructor will select the randomization button in REDCap while they are still on the phone with the subject. Once the button is selected, the live feedback from REDCap will display the assigned group. In the same phone call (using a Randomization Script), the SME instructor will immediately inform the subject of the details of their group assignment, give them a brief pre-orientation of the program, and provide the subject with:
  - Welcome information
  - Their instructors' names (Update at each wave)
  - Their instructors' contact information (Update at each wave)
  - The Zoom Information for their class, and guidance on how to use Zoom. All MBSR and SME sessions will be conducted via Penn State University (PSU) Zoom.
  - The times and dates of their 14 study sessions (Update at each wave):
    - ❖ Orientation session that will last 1 and a half to 2 hours (1 session).
    - ❖ Class #1 to 8: These sessions are once a week during the first 8 weeks, starting approximately 1 week after Orientation. The duration for each of these sessions will be 2 and a half to 3 hours (8 sessions).
    - ❖ Retreat: A single longer MBSR or SME session that will last 7 hours (1 session)
    - ❖ Booster sessions #1 to 4: These are 45-minute long MBSR or SME booster sessions every month in Months 3, 4, 5 and 6 (4 sessions).
    - ❖ Attendance will be recorded at each session. Subjects will be instructed to let their instructor know if they need to be excused from a session. It is possible that for some unforeseen reason a subject misses a session. If this happens, the subject may not be able to make the session up, but they will be encouraged to continue to follow along with the home practice and do their best to attend all the remaining sessions that they are assigned to.
  - After speaking with the subject and providing them with an overview of their group assignment via phone, the SME instructor will email the subject the details of their group assignment (See SME Instructor Email Template Randomized to MBSR and SME Instructor Email Template Randomized to SME).
- The SME instructor will inform the subjects that after Class #8, they will start receiving emails inviting them to participate in additional Retreat sessions and monthly booster sessions (See SME Instructor Email Template After Class #8 MBSR Booster Reminder and SME Instructor Email Template After Class #8 SME Booster Reminder). The monthly booster sessions in months 3 to 6 are required sessions for the study. The remaining booster sessions, and any additional Retreat sessions after Class #8, are optional sessions that subjects may choose to participate in if they wish. Attendance will be recorded at these additional sessions, however subjects will not receive any financial compensation for participating in the optional sessions.
- Subjects will be advised to contact their instructor if they have any questions or concerns about their sessions or home practice.
- The SME instructor will remind the subject that the above information should ONLY be discussed with their course instructor (unblinded staff members), and should not be discussed with the blinded research coordinators or any other study staff that they communicate with at study visits or via phone calls who are blinded to group assignments.

- The SME instructor will provide the subject with their own contact information so if the subject has any questions about the above they can contact the SME instructor. The SME instructor will need to agree to be easily accessible to any and all subjects that contact them with questions pertaining to their study group.
- The SME instructor will answer any questions subjects may have during the Randomization phone call.
- The name of the SME instructor will be captured within REDCap each time they randomize a subject as the SME instructor randomizing subjects is subject to change with each cohort/wave.

Additional procedures the SME instructor will complete during the week before Orientation:

- Before 8 AM on the day of the Orientation, the SME instructor will send (via Secure File Transfer - SFT) the list of randomized MBSR subjects with their contact information (Name, Email Address, Phone Number) to the MBSR instructors.

Other study procedures the SME instructor will complete:

Once an SME instructor randomizes a subject to MBSR or SME, that SME instructor will be responsible for following that subject throughout the time that the subject is in the study, and completing any study procedures that cannot be completed by the blinded research coordinators, including:

- By Class #1, record the number of subjects in their cohort randomized to each group (and any other needed information) in the Unblinded Classes sheet in the Excel Study Tracking Spreadsheet in Google Drive. This information will be used by unblinded research team members e.g. the SME instructors, to check that the correct number of subjects started up the MBSR and SME Daily Diary surveys after Class #1. Blinded study team members cannot be aware of the number randomized to each group in a cohort since this could reveal group assignments.
- Coordinate the documentation of attendance at the MBSR or SME sessions for each subject in their cohort (See the section below entitled “Attendance”)
- To encourage subject retention in the study, and to parallel what is commonly done in MBSR, after Class #8, the instructors will invite the subjects to participate in additional MBSR or SME Retreat sessions and monthly booster sessions (See SME Instructor Email Template After Class #8 MBSR Booster Reminder and SME Instructor Email Template After Class #8 SME Booster Reminder). The monthly booster sessions in months 3 to 6 are required sessions for the study. The remaining booster sessions, and any additional Retreat sessions after Class #8, are optional. Attendance will be recorded at these additional sessions, however subjects will not receive any financial compensation for participating in the optional sessions.
- The SME instructor will serve as the point-of-contact for any and all communications between the MBSR/SME instructors and the blinded research team about subjects in a manner that does not reveal a subject’s group assignment (See the section below entitled “Blinding”).
- A subject’s SME instructor will be the one main point person that the subject can contact with any questions about the study. This will be very important in building rapport with the subject and encouraging retention in the study.
- Any other study procedures that cannot be completed by the blinded research coordinators.

Attendance:

The SME instructor for each cohort/wave will coordinate the documentation of attendance for each MBSR and SME subject in their cohorts throughout the 6 months that the subjects are in the study. Subjects’ attendance will be documented for the Orientation session, Class #1 to 8, the Retreat session, Booster sessions #1 to 4, and

any additional optional study booster sessions and retreat sessions that subjects participate in while they are in the study. Attendance will be recorded by the MBSR or SME instructor at the beginning of each Zoom session. For the purposes of this study, 'attendance' is defined as attending the class in full, entering the class late, and/or leaving the class early (e.g. partial attendance will count as full attendance).

Within 24 hours of each session, the SME instructors will record the attendance for each of the MBSR and SME subjects, in the Blinded Attendance Log in REDCap. Blinded study team members will be able to review the Blinded Attendance Log as it will not contain any information that would reveal group assignments.

Procedures for when a subject misses a session: The protocol for contacting subjects who miss a session will be similar for both MBSR and SME groups. The following procedures will be completed when a subject misses an MBSR or SME session that they are assigned to:

- If a subject misses the Orientation session after being randomized, the subject's instructor (either MBSR or SME) will contact the subject and offer them an individual Orientation session. If a subject does not complete Orientation after being randomized to MBSR or SME prior to Class #2, the SME instructor will notify the research coordinator and the subject will be withdrawn from the study.
- If a participant misses a Class #1 to 8 session, Retreat session or booster session, the subject's instructor (either MBSR or SME) will complete the following procedures:
    - Send a follow-up email if someone misses a class and let them know we missed them.
    - Encourage them to continue to follow along with the home practice and do their best to attend all the remaining sessions that they are assigned to.
    - Offer to be available by email, phone call, or schedule a time to meet usually before or after the next class, if they wish to have a private discussion.
    - The SME instructor will ask the MBSR instructor to let them know if they receive any communication from a study participant regarding a missed session.
- After 48 hours of the missed session, if a study participant in MBSR or SME, has not communicated with the instructors regarding a missed session, the SME instructor will call the participant.
- Each MBSR and SME instructor will keep a Participant Contact Log, where they record each time they attempt to contact a study participant in MBSR or SME (via phone or email) for missing a session. Each instructor will maintain their Participant Contact Log securely themselves, and they will hand this log in to the research team at the end of the study. If the research team needs any information on this log before then, the MBSR instructor will securely share their log with the SME instructor who will securely share the needed information with the research team in a blinded manner. This log will include the following for each contact attempt:
    - Date and time of each contact attempt
    - Whether the contact attempt was via phone or email
    - Whether or not the subject responded (confirming successful contact), and if the subject responded:
        - ❖ Date of subject response
        - ❖ Whether the subject's response was via phone or email
        - ❖ Any reasons the subject provided for missing the session, and
        - ❖ Whether the subject confirmed that they will or will not be attending the subsequent sessions.
- If a subject has 2 consecutive unexcused absences from MBSR or SME, the SME instructor or other unblinded research coordinator will contact the subject, and encourage the subject to continue to follow along with the home practice and do their best to attend the sessions. Subjects will be advised to contact their instructor if they have any questions or concerns about their sessions or home practice.

Blinding:

The PI, research coordinators and all other research team members involved in the collection or review of outcomes data will be blinded. The random assignment of subjects to MBSR or SME will not be communicated to any research team member who will be collecting or reviewing outcomes data. The subjects, SME instructors, MBSR instructors, data manager, video coders, Dr. McCown will be asked to keep the study group assignments concealed from the blinded investigators and study personnel.

The SME instructors, MBSR instructors, and other unblinded research team members will be asked not to reveal the number of study subjects in an MBSR course, or in an SME course, to the research coordinators and other blinded research team members.

The research coordinators and other blinded research team members will be:

- Blinded to the number of subjects randomized to MBSR in a cohort/wave
- Blinded to the number of subjects randomized to SME in a cohort/wave

The research coordinators and other blinded research team members will be:

- Aware of the total number of subjects randomized in a cohort/wave

Subjects will be asked to keep their study group assignment concealed from the blinded study personnel, including the research coordinators and other study personnel that they meet during the study visits. At the beginning of any phone call, study visit, or other contact with a subject, blinded research team members will remind subjects not to say anything that would reveal their group assignment e.g. instructors' names, specifics about their classes or Daily Diary survey questions, the PSU Zoom link for their classes, etc.

The research coordinators and other blinded research team members will not have access to the Experience Sampling Surveys in REDCap, which will be managed by unblinded research team members e.g. the SME instructors. Additionally, the PSU Zoom links for the classes will only be available to Dr. McCown and the instructors as these individuals will not be blinded.

Procedures in the MBSR group will parallel procedures in the SME group to maintain blinding. As an example, since subjects in the MBSR group are not allowed to continue with MBSR if they miss Orientation, the same will apply for subjects in the SME group. Additionally, if a session for one group needs to be canceled for any reason, the concurrent session for the other group will also be canceled.

The SME instructors will serve as the point-of-contact for any and all communications between the MBSR/SME instructors and the blinded research team about subjects, in a manner that does not reveal a subject's group assignment. The MBSR instructors and SME instructors will be given each other's contact information. Any subject-specific information, including any potential adverse events that an instructor becomes aware of in an MBSR subject, or in an SME subject, (e.g. requiring a change in MBSR or SME practice recommendations), will be communicated to the blinded research coordinator through the SME instructors, in a manner that does not reveal the subject's group assignment. The MBSR instructors will avoid directly communicating with the blinded research coordinator and other blinded research team members about specific subjects. The MBSR instructors will directly communicate information about MBSR subjects to the SME instructors. The SME instructors will communicate information about MBSR subjects and SME subjects to the blinded research coordinator in a manner that does not reveal which

instructor the subject reported the adverse event to or any other information that would reveal the subject's group assignment. To accomplish this, we will minimize the 'discussion' aspect of how the SME instructors report potential adverse events or any other information about a subject to the research coordinator because discussion of the report may lead to unblinding/may make it obvious as to which instructor it was reported to if the SME instructor doesn't know much about the encounter. The SME instructors will simply state e.g. "Participant ID 123 has reported <a symptom or potential adverse event or other information worded in a manner that does not reveal the subject's group assignment> to an instructor." The research coordinator will then follow up with the subject via phone for formal adverse event documentation. If indicated, the research coordinator will complete an Adverse Event form. Similarly, any subject-specific information that the research coordinators need to communicate to the instructors will go through the SME instructors, and then the SME instructors will pass the information along to the MBSR instructors if the subject is in the MBSR group.

Blinded research team members will not participate in any of the study MBSR or SME sessions.

Subject Expectancy: To minimize the influence of subjects' expectations, subjects will be informed that the study is designed to test the effects of two different types of stress reduction programs, one of which is combined with health education. Subjects will be informed that they will be asked to participate in one or more of the following activities during the study sessions: breathing exercises, meditation, stretching exercises or health education activities. Further, subject expectancy will be assessed at the baseline, 2-month, and 6-month, study visits using a Stress Reduction Expectancy Scale (SRES) modified from the Acupuncture Expectancy Scale.

MBSR Intervention and Stress Management Education (SME) control:

Once subjects are assigned to a study group, they will participate in 14 MBSR or SME control sessions:

- Orientation session that will last 1 and a half to 2 hours depending on the duration of the individual participant interviews (1 session).
    - Subjects will be informed that they must attend the Orientation session to continue in the study. If a subject misses the Orientation session after being randomized, the subject's instructor will contact the subject and offer them an individual Orientation session. If a subject does not complete Orientation after being randomized to MBSR or SME, the SME instructor will notify the research coordinator and the subject will be withdrawn from the study.
- Class #1 to 8: These sessions are once a week during the first 8 weeks, starting approximately 1 week after Orientation. The duration for each of these sessions will be 2 and a half to 3 hours (8 sessions).
- Retreat: A single longer MBSR or SME session that will last 7 hours (1 session)
- Booster sessions #1 to 4: These are 45-minute long MBSR or SME sessions every month in Months 3, 4, 5 and 6 (4 sessions).

All MBSR and SME sessions will be delivered online by experienced instructors in a live interactive virtual classroom using videoconferencing (PSU Zoom). Participants will be asked to find a place in their homes where they will not be disrupted during the sessions.

MBSR and SME sessions will be held in small groups. The number of sessions will be the same in MBSR and SME to control for instructor attention and group support.

Attendance will be recorded at each session (See above section on Attendance). Subjects will be instructed to let their instructor know if they need to be excused from a session. It is possible that for some unforeseen reason a subject misses a session. If this happens, the subject may not be able to make the session up, but they will be encouraged to continue to follow along

with the home practice and do their best to attend all the remaining sessions that they are assigned to (See above section on "Procedures for when a subject misses a session").

After Class #5: Subjects will be sent a link from REDCap to complete the MBSR or SME Midway Check-in form.

After Class #8: Subjects will be sent a link from REDCap to complete the MBSR or SME Final Class Assessment form.

After Class #8, subjects will start receiving emails inviting them to participate in additional MBSR or SME Retreat sessions and monthly booster sessions. The monthly booster sessions in months 3 to 6 (Booster sessions #1 to 4) are required sessions for the study. The remaining booster sessions, and any additional Retreat sessions after Class #8, are optional sessions subjects may choose to participate in if they wish. Attendance will be recorded at these additional sessions, however subjects will not receive any financial compensation for participating in the optional sessions. By keeping subjects informed of additional MBSR or SME booster and Retreat sessions after Class #8, these emails will be important for subject retention in the study.

We will be comparing MBSR alone versus SME alone. The MBSR group will not receive SME. The SME group will not receive any mindfulness.

MBSR and SME Home Practice: Subjects in both the MBSR and SME groups will be asked to do at least 25 to 30 minutes of home practice per day for 6 out of 7 days per week. Positive clinical outcomes and high adherence have been reported with 25 to 30 minutes per day of MBSR home practice, which is a common adaptation to the standard 45 minutes per day of MBSR home practice.

Home practice in MBSR will consist of mindfulness activities in accordance with the standard MBSR curriculum. Home practice in SME will consist of listening to excerpts of audiobooks about general stress management or nutrition facts.

Instructors will assign home practice for the first 7 weeks of MBSR and SME, starting after Class #1. There will be no home practice assignments after Class #8, however after Class #8 subjects will be encouraged to continue their home practice activities regularly on their own. The Daily Diary survey will be administered daily throughout the study to measure the type and quantity of home practice.

MBSR intervention group: Subjects randomized to MBSR will receive the 8-week University of Massachusetts MBSR curriculum (Santorelli et al., 2017), adapted for live online delivery due to the COVID-19 pandemic, followed by live online mindfulness booster sessions every month in Months 3 to 6. The University of Massachusetts MBSR curriculum was selected for the intervention as it is the most standardized and researched mindfulness program that has been shown to reduce psychological distress in various patient populations (Kabat-Zinn, 1990). Any updates to the University of Massachusetts MBSR curriculum will be implemented as soon as they become available, and it will be documented at what point in the study they were implemented. To optimize delivery of MBSR in the proposed study, the MBSR sessions will be led by Donald McCown, PhD, MAMS, MSS, LSW, or another experienced MBSR instructor (e.g. Holly Socolow) who will receive regular supervision from Dr. McCown. Dr. McCown is the first author of "Teaching Mindfulness: A Practical Guide for Clinicians and Educators" (McCown et al., 2010). Prior to leading MBSR sessions in the study, MBSR instructors will have completed the University of Massachusetts MBSR Practice Teaching Intensive or its equivalent. Additionally, the study MBSR instructors have been provided with resources to supplement their teacher training with meditation safety and trauma informed mindfulness, including the Meditation Safety Toolbox (https://www.brown.edu/research/labs/britton/resources/meditation-safety-toolbox) and Trauma-Sensitive Mindfulness (https://davidtreleaven.com/).

Outline of MBSR Booster Sessions:

- Minutes 1 to 10 - Socializing
- Minutes 11 to 20 - Didactic on topic based on MBSR (Instructors will keep a log of topics discussed with dates)
- Minutes 21 to 35 - Mindfulness practice
- Minutes 36 to 45 - Discussion regarding practice

Stress Management Education (SME) control group: Subjects randomized to the SME control group will receive Dr. Elizabeth Hoge's Stress Management Education (SME) program, adapted for live online delivery due to the COVID-19 pandemic. Stress Management Education was specifically created as a control condition for MBSR studies so it matches MBSR for time, social support, homework, etc. (Hoge et al., 2013). Stress Management Education does not have any mindfulness in it. The instructors for the SME sessions will have prior experience working with groups and they will be trained by Dr. Hoge to teach SME in the study. Dr. Hoge will continue to be available throughout the study in case any questions arise about SME. The SME program includes nutrition (which will be adapted for the diabetes population), exercise as gentle stretching with Theraband to match yoga in MBSR, and other general health topics that may be relevant to the diabetes population such as sleep, time management, etc. Homework for the SME control group will be excerpts of audiobooks about general stress management or nutrition facts. The SME control group will follow a manualized intervention, be optimized in its appeal to subjects, and have regular supervision and facilitator buy-in just like the MBSR group, as is recommended for active controls for MBSR studies (MacCoon et al., 2012). The SME control group will not involve any mindfulness.

Subjects in both the MBSR and SME groups will have received the same general written guidelines on diet and exercise at their baseline study visit, consisting of two handouts downloaded from the American Diabetes Association Patient Education Library: (1) “Plan Your Portions” Diabetes Placemat and (2) “The Diabetes Advisor - Physical Activity.” All subjects will have also received handouts on Hyperglycemia and Hypoglycemia, as well as Glucometer Best Practices and Blood Glucose Meter Correlation, at their baseline study visit. This will be the only information that will be the same across both groups. The MBSR group will not receive any additional health education other than these handouts. Throughout the duration of the study, the SME control group’s education on diet and physical activity will not include mindfulness, but will be focused on physical benefits. Only the MBSR group will engage in mindful walking and yoga, and mindful eating, which involves bringing awareness to emotions, cognitions, and physical sensations while engaged in these activities. For participants unable to walk, appropriate adjustments and modifications can be made.

Subject Adherence:

Adherence to the intervention will be emphasized to all subjects. Those who cannot commit with reasonable certainty to the intervention will not be randomized. If a subject thinks they will miss the Orientation, or if they think they will miss more than 2 classes during the first 8 weeks (including Class #1 to 8 and the Retreat), they will be encouraged to wait for another wave/cohort when they are able to make the time commitment. Attendance will be recorded at each MBSR or SME control session as described in the section above entitled “Attendance.” In addition, adherence may be reflected in changes in mindfulness which will be assessed with the validated Toronto Mindfulness Scale (TMS; 13 items).

Feasibility will be determined by successful recruitment and retention of subjects in the study. Successful delivery of MBSR will be demonstrated through increased measures of mindfulness (TMS) in the MBSR group, and the daily MBSR home practice log (Daily Diary survey). The TMS will be particularly useful in assessing subject's mastery of MBSR skills

Retention of Subjects:
We will use the following strategies to keep subjects engaged throughout the 6 months of the study.

We will offer a new cohort of MBSR and SME control classes approximately every 3 months (4 times a year). We do not anticipate subjects waiting more than 3 months to start a class, except over the summer when wait time may be slightly longer due to vacations and scheduling challenges. We will keep potential study subjects engaged from the start by providing them with the dates and times for the next cohort of classes. Providing the dates and times of the classes early on will keep potential subjects engaged and it will also allow them to plan ahead and begin to make room in their schedule.

Study visits will be scheduled as much as possible in advance, taking into account when subjects will be most available, especially around busy times like holidays, vacations, etc. We will also keep potential subjects engaged by scheduling them for screening in the 10 weeks and 2 days (72 days) before the start of the study intervention (Orientation). Those who meet the eligibility criteria and consent will be kept further engaged by scheduling them for a baseline study visit in the 6 weeks before the start of the study intervention (Orientation).

Subjects will be randomized in the week before the start of the study intervention (Orientation). At that time, the SME instructor will contact the subject by phone to randomize them after answering any questions the subject may have and confirming that the subject is still available to participate in the study.

The SME instructor who randomizes a subject will be the one main point person that the subject can contact with any questions about the study. This will be very important in building rapport with the subject and encouraging retention in the study.

Research staff will contact subjects throughout the study to encourage retention, including:

- The research coordinators will call subjects before each of their remote or in-person study visits to review instructions for the study visit and remind subjects to bring their smartphone, glucometer (even if not checking blood sugars frequently), other diabetes devices (e.g. CGM, insulin pump or other smart insulin delivery devices), Home A1cNow Self Check kit, accelerometer if indicated, current medication list, etc. The research coordinators will also ask subjects for the names of any new diabetes devices (glucometers, CGM, insulin pump or other smart insulin delivery devices) they have been using since the previous study visit so that the research team can plan how to collect data from the new device at the upcoming study visit.
- If a subject misses a study visit, the research coordinators will call the subject to reschedule the study visit within the specified time window if possible, and to confirm the subject is still willing to come to subsequent study visits (See Overview of Study Visit Time Windows above in section 7.2.2).
- After Class #8, subjects will start receiving emails inviting them to participate in additional MBSR or SME Retreat sessions and monthly booster sessions. The monthly booster sessions in months 3 to 6 (Booster sessions #1 to 4) are required

sessions for the study. The remaining booster sessions, and any additional Retreat sessions after Class #8, are optional sessions subjects may choose to participate in if they wish. Attendance will be recorded at these additional sessions, however subjects will not receive any financial compensation for participating in the optional sessions. By keeping subjects informed of additional MBSR or SME booster and Retreat sessions after Class #8, these emails will be important for subject retention in the study.

- The SME instructors or unblinded research coordinators will call subjects before each of the required MBSR and SME booster sessions (Booster sessions #1 to 4) to remind subjects of the booster sessions and to encourage them to do their best to continue to respond to the Stress & Cravings and Daily Diary survey invitations, check their blood sugars as prescribed, etc.
- If a subject misses an MBSR or SME session that they were assigned to, the subject will receive an email from their instructor. After 48 hours of the missed session, if the subject has not communicated with the instructors regarding the missed session, the SME instructor will call the subject. Subjects who miss a session will be encouraged to continue to follow along with the home practice and do their best to attend all the remaining sessions that they are assigned to.
    - If a subject has 2 consecutive unexcused absences, the SME instructor or other unblinded research coordinator will contact the subject, and encourage the subject to continue to follow along with the home practice and do their best to attend the sessions. Subjects will be advised to contact their instructor if they have any questions or concerns about their sessions or home practice.
- The SME instructor or unblinded research coordinators will call subjects if the response rate to the Stress & Cravings or Daily Diary survey is less than 70% (or 0% meaning no responses at all) as described in the section above entitled “Experience Sampling: Daily Stress & Cravings and Daily Diary Surveys.”
- Whenever possible more than one of the above can be carried out in a single phone call.

At the beginning of any phone call, study visit, or other contact with a subject, blinded research staff will remind subjects not to say anything that would reveal their group assignment e.g. instructors’ names, specifics about their classes or Daily Diary survey questions, the PSU Zoom link for their classes, etc.

At every contact with a subject (e.g. phone call, study visit), the research staff will encourage retention of the subjects by including the following principles:

1- Appreciation: Research staff will let the subjects know that we appreciate all that they are doing for the study.
2- Encouragement without judgment: Research staff will encourage subjects to attend all the study visits and will reassure subjects that they will not be judged if they are not able to check their blood sugars as prescribed or respond to all the Experience Sampling Surveys, or if they miss a class etc. Subjects will be encouraged to do their best to complete as many of the classes and study procedures as they are able to.
3- Purpose: We will engage all the subjects with the goals of the research and explain how every study visit and every study procedure they complete are very important in helping the research team better understand how stress affects people living with diabetes.

7.2.5 Visit #2 (Follow-up Phone Call after Class #4)

Within 2 weeks after Class #4, the blinded research coordinators will call the subjects and administer the Stress Experience Survey and the Hypoglycemia Survey using a phone script. At the beginning of the phone call, the research coordinator will remind subjects not to say anything that would reveal their group assignment e.g. instructors' names, specifics about their classes or Daily Diary survey questions, the PSU Zoom link for their classes, etc. The research coordinator will make 3 attempts to reach a subject for the follow-up phone call. If a subject misses the follow-up phone call within the specified 2-week time window, the subject will not be withdrawn from the study, and their follow-up phone call data will be considered missing data.

7.2.6 Visit #3 (2-month Study Visit)

The 2-month study visit will be scheduled after MBSR or SME Class #8. If the 2-month visit cannot be completed in the CRC due to COVID-19, or the preference of the subject, the 2-month visit will be completed remotely using videoconferencing (PSH Teams), and all data that can be collected remotely will be obtained including the home hemoglobin A1c using the Home A1CNow Self Check kit, urine pregnancy test when applicable, diabetes device data, and surveys. At the beginning of the study visit, the blinded research coordinators will remind subjects not to say anything that would reveal their group assignment e.g. instructors' names, specifics about their classes or Daily Diary survey questions, the PSU Zoom link for their classes, etc.

Subjects will be asked to bring the following to the remote or in-person 2-month visit:

- A list of their current medications and supplement so their current medications and supplements can be recorded
- Their smartphone if they have one
- Their diabetes devices (glucometers, CGM, insulin pump and other smart insulin delivery devices)
- Home A1cNow Self Check kit they were given at their screening or baseline visit.

At the 2-month study visit, subjects will present to the CRC after a 10-hour fast (no food or drink, except for water). Additionally, subjects will be asked not to eat or drink (except for water), chew gum, smoke, brush their teeth, exercise physically, or consume prescription or over-the-counter medications in the 60 minutes prior to the visit (as well as during the last 60 minutes of the visit) to prepare for the collection of saliva samples. Subjects will be asked not to wash their hair for 24 hours before the visit, and not to have their hair cut to a length less than 2 cm, to prepare for the optional collection of 2 cm hair samples. Subjects will be asked not to clip their fingernails for at least 2 to 3 weeks prior to the visit to prepare for the optional clipping of approximately 2 mm of nails from each finger of both hands. Subjects will be asked to remove any nail polish at least 24 hours before the visit.

At the 2-month visit, the procedures in the baseline visit will be repeated as described above in section 7.2.3 entitled "Visit #1 (Baseline Study Visit)" and in **Table 3**. In the CRC, a single blood sample will be obtained and all of the baseline laboratory measurements will be repeated. If a subject forgets to fast, blood will still be drawn and documentation will be made of how many hours it has been since they last had something to eat or drink. Saliva for cortisol and α-amylase will be collected 1) Just before the study visit starts, and 2) immediately after the study visit ends. Hair and nail samples (optional) will be collected and stored to be analyzed later for cortisol, but they will not be analyzed under this protocol. Physical exam will include measurement of weight, height, waist and hip circumferences, blood pressure, and pulse. Body composition will be measured using a Tanita scale, when possible. The physical exam will only be completed if the study visit is in the CRC.

All subjects will complete self-administered questionnaires as described in the baseline visit. After sitting quietly for 15 minutes they will first complete the Toronto Mindfulness Scale (TMS). Then they will complete the remaining questionnaires: Stress Reduction Expectancy Scale (SRES), Food Craving

Questionnaire-Trait-Reduced (FCQ-TR), Walking Enjoyment Scale, Participant Questionnaire, Diabetes Distress Scale (DDS), Perceived Stress Scale-10 (PSS-10), Short Form-12 (SF-12), Positive and Negative Affect (PANAS), GAD-7, PROMIS-Sleep Disturbance 8a, Modified Coronavirus Impact Scale, Phone Call Time Preference, and the safety assessment PHQ-9. The Counterfactual Measurement will not be administered at the 2-month visit as this questionnaire has a 6-month recall period and will only be administered at the baseline and 6-month study visits.

In addition, subjects will be asked to rate their Perceived Efficacy, Satisfaction, Engagement and Confidence in the study sessions, on a scale of 0-10 (0 = Not at all; 5 = Moderately; 10 = Very much). These questions will be self-administered at the 2-month study visit (as well as at the 6-month study visit). These items were adapted from a previous acupuncture study (Mao et al., 2007).

The research coordinators will administer the Stress Experience Survey and the Hypoglycemia Survey, collect glucometer, CGM and diabetes device data, and assist the subjects in obtaining their home hemoglobin A1C value from the Home A1cNow Self Check kit as described in the baseline visit. Additionally, the research coordinator will record whether the subjects responded to at least 70% of the Daily Diary and the Stress and Cravings Experience Sampling Surveys.

At the end of the 2-month visit, a urine pregnancy test will be administered to female subjects of childbearing potential who do not meet any of the criteria for reasonable certainty of not being pregnancy as defined above in the screening visit. Any subjects found to be pregnant will be informed of their pregnancy test results, and then withdrawn from the study due to the effects of pregnancy on study outcomes. If the subject has a pregnancy test within 2 weeks before the 2-month visit, verified in their medical records, the pregnancy test result can be accepted in lieu of repeating the test at the 2-month visit. If the study visit is conducted remotely, and if a pregnancy test result collected within 2 weeks before the study visit is not available, then the subject will be mailed a urine pregnancy test to complete at this visit. Subjects will communicate their urine pregnancy test result to the study team by showing the research coordinator their pregnancy test result as displayed on their urine pregnancy test kit during the (PSH Teams) live videoconferencing study visit. If the pregnancy test is positive, the subject will be withdrawn from the study.

At the 2-month visit, the research coordinators will provide subjects with an optional Actigraph device to wear around their waist for 7 days after the visit. If the 2-month visit is conducted remotely, the optional Actigraphs will be mailed to the subject. Subjects will be asked to mail the Actigraph back to the study team, after the 7 day wear time, in a pre-stamped envelope, along with a wear time log/diary. In the 2 weeks after Class #8, subjects will receive email invitations from the research coordinator to complete two optional ASA24 dietary recalls (1 weekend and 1 weekday) about their food intake on the previous day.

If a study visit is conducted remotely, or if a subject misses a study visit, the research coordinator will obtain and record any available diabetes device data and outside lab results, including hemoglobin A1c, glucose and Lipid panel.

7.2.7 Visit #4 (6-month Study Visit/End of Study Visit)

The 6-month study visit will be scheduled after MBSR or SME Booster session #4 (end of study). If the 6-month visit cannot be completed in the CRC due to COVID-19, or the preference of the subject, the 6-month visit will be completed remotely using videoconferencing (PSH Teams) and all data that can be collected remotely will be obtained including the home hemoglobin A1c using the Home A1CNow Self Check kit, urine pregnancy test when applicable, diabetes device data, and surveys. At the beginning of the study visit, the blinded research coordinators will remind subjects not to say anything that would

reveal their group assignment e.g. instructors' names, specifics about their classes or Daily Diary survey questions, the PSU Zoom link for their classes, etc.

Subjects will be asked to bring the following to the remote or in-person 6-month visit:

- A list of their current medications and supplements so their current medications and supplements can be recorded
- Their smartphone if they have one
- Their diabetes devices (glucometers, CGM, insulin pump and other smart insulin delivery devices)
- Home A1cNow Self Check kit they were given at their screening or baseline visit
- The optional Actigraph device and wear time log/diary that was mailed to them before this visit so that they could wear the Actigraph for 7 days before the final visit

At the 6-month study visit, subjects will present to the CRC after a 10-hour fast (no food or drink, except for water). Additionally, subjects will be asked not to eat or drink (except for water), chew gum, smoke, brush their teeth, exercise physically, or consume prescription or over-the-counter medications in the 60 minutes prior to the visit (as well as during the last 60 minutes of the visit) to prepare for the collection of saliva samples. Subjects will be asked not to wash their hair for 24 hours before the visit, and not to have their hair cut to a length less than 2 cm, to prepare for the optional collection of 2 cm hair samples. Subjects will be asked not to clip their fingernails for at least 2 to 3 weeks prior to the visit to prepare for the optional clipping of approximately 2 mm of nails from each finger of both hands. Subjects will be asked to remove any nail polish at least 24 hours before the visit.

At the 6-month visit, the procedures in the baseline visit will be repeated as described above in section 7.2.3 entitled "Visit #1 (Baseline Study Visit)" and in **Table 3**. In the CRC, a single blood sample will be obtained and all of the baseline laboratory measurements will be repeated. If a subject forgets to fast, blood will still be drawn and documentation will be made of how many hours it has been since they last had something to eat or drink. Saliva for cortisol and α-amylase will be collected 1) Just before the study visit starts, and 2) immediately after the study visit ends. Hair and nail samples (optional) will be collected and stored to be analyzed later for cortisol, but they will not be analyzed under this protocol. Physical exam will include measurement of weight, height, waist and hip circumferences, blood pressure, and pulse. Body composition will be measured using a Tanita scale, when possible. The physical exam will only be completed if the study visit is in the CRC.

All subjects will complete self-administered questionnaires as described in the baseline visit. After sitting quietly for 15 minutes they will first complete the Toronto Mindfulness Scale (TMS). Then they will complete the remaining questionnaires: Stress Reduction Expectancy Scale (SRES), Food Craving Questionnaire-Trait-Reduced (FCQ-TR), Walking Enjoyment Scale, Participant Questionnaire, Diabetes Distress Scale (DDS), Perceived Stress Scale-10 (PSS-10), Short Form-12 (SF-12), Positive and Negative Affect (PANAS), GAD-7, PROMIS Sleep Disturbance 8a, Modified Coronavirus Impact Scale, the safety assessment PHQ-9, and Counterfactual Measurement. In addition, questions about Perceived Efficacy, Satisfaction, Engagement and Confidence in the study sessions will be self-administered at the 6-month study visit as described in the 2-month study visit.

The research coordinators will administer the Stress Experience Survey and the Hypoglycemia Survey, collect glucometer, CGM and diabetes device data, and assist subjects in obtaining their home hemoglobin A1c value from the Home A1cNow Self Check kit as described in the baseline visit.

At the end of the 6-month visit, a urine pregnancy test will be administered to female subjects of childbearing potential who do not meet any of the criteria for reasonable certainty of not being pregnant as defined above in the screening visit. Any subjects found to be pregnant will be informed of their pregnancy test results. If the subject has a pregnancy test within 2 weeks before the 6-month visit,

verified in their medical records, the pregnancy test result can be accepted in lieu of repeating the test at the 6-month visit. If the study visit is conducted remotely, and if a pregnancy test result collected within 2 weeks before the study visit is not available, then the subject will be mailed a urine pregnancy test to complete at this visit. Subjects will communicate their urine pregnancy test result to the study team by showing the research coordinator their pregnancy test result as displayed on their urine pregnancy test kit during the (PSH Teams) live videoconferencing study visit.

Before the 6-month visit, the research coordinators will mail subjects an optional Actigraph device to wear around their waist for 7 days before the visit. Subjects will be asked to return the Actigraph and wear time log/diary at the 6-month visit. If this visit is conducted remotely, subjects will be asked to mail the Actigraph back to the study team, after the 7 day wear time, in a pre-stamped envelope, along with a wear time log/diary. In the 2 weeks before Booster #4, subjects will be emailed by the research coordinator and asked to complete two optional ASA24 dietary recalls (1 weekend and 1 weekday) about their food intake on the previous day.

If a study visit is conducted remotely, or if a subject misses a study visit, the research coordinator will obtain and record any available diabetes device data and outside lab results, including hemoglobin A1c, glucose and Lipid panel.

7.3 Duration of Participation

The duration of an individual subject's participation in the study will be approximately 6 to 8-1/2 months.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

The number of subjects expected to be enrolled and screened is no more than 520 subjects in order to reach the randomization target of 290 subjects. To assure reaching the study's planned sample size requirement (of 290) we will randomize no more than 320 subjects in total.

8.2 Sample size determination

The primary outcome for this trial is the absolute difference between the two interventions with respect to the mean change in hemoglobin A1c from baseline to month 6 and we consider an absolute difference of 0.5% in this outcome to be clinically meaningful. As this is an individually randomized group treatment trial, correlation among observations within groups (defined here as class cohort), as measured by the intraclass correlation coefficient (ICC), must be taken into consideration (Pals et al., 2008). The variance inflation factor, or design effect, for this type of trial will inflate the sample size by $1+(1-m)\rho$, where m is the average group size and ρ is estimated by the ICC. For both interventions (MSBR and SME), we plan to have the average group size be 18 subjects and expect the ICC=0.08. Thus, the design effect is 2.36. Furthermore, we anticipate that 15% of the subjects will drop-out of the study prior to completion. Incorporating the design effect of 2.36 and the anticipated 15% drop-out, a sample size of 290 subjects (145/intervention) will provide 80% power to detect a clinically meaningful 0.5% absolute difference between the two interventions with respect to the mean change in hemoglobin A1c from baseline to month 6, assuming a standard deviation of 0.9% (Frias et al., 2011) using a two-sided test having a significance level of 0.05.

8.3 Statistical methods

Data (i.e., physiologic, behavioral, diabetes-related distress, and mindfulness) will be collected longitudinally in this trial. The time period of primary interest in this trial is the change from baseline to

6-months. Linear mixed effects models, which are subject-specific models, will be fit and contrasts constructed to assess adjusted changes from baseline between interventions over time with respect to these continuous outcomes (e.g., the primary outcome of hemoglobin A1c). The primary contrast of interest is the change in an outcome from baseline to month 6 between the two interventions. However, contrasts will also be constructed to assess the change in an outcome from baseline to other points in time (e.g., month 2) between the two interventions to gauge, for example, if the intervention is effective at month 2. The independent fixed factors for the mixed-effects models will include intervention, time (e.g., baseline, 2 months, 6 months), the randomization stratification factor of insulin vs. non-insulin treated at baseline, and the interaction of intervention with time. The group (class cohort) the participant is assigned will be a nested random effect (i.e., group/class cohort will be nested within intervention) in the mixed-effects models to account for the correlation among observations within groups (class cohorts) inherent in an individually randomized group treatment trial (Pals et al., 2008; Murray et al., 2004). Each class cohort will be characterized by various class sizes, instructors, etc. and thus will be important to account for throughout the duration of the trial wherever possible. The time factor in the models for the vast majority of the outcomes will consist of measurements taken at baseline, 2 months, and 6 months, per subject. An unstructured variance-covariance matrix will be pursued to assess the residual error associated with the repeated measurements over time per participant. If this variance-covariance structure fails to provide model convergence, then others will be explored. Linear mixed-effects models are an extension of ordinary regression models that account for the between- and within-subject correlation inherent in longitudinal trials. Mixed-effects models also appropriately handle the correlation within groups for individually randomized group treatment trials by specifying these groups as random effects. Residual diagnostics will be used to determine the appropriateness of model fit and, if necessary, transformations (e.g., logarithmic) of the outcome will be performed to meet modeling assumptions. If transformations fail to provide adequate model fit then adding splines to the linear mixed-effects models, or using nonlinear mixed-effects models, will be considered.

Following our assessment of the initial fit of the models, we will add covariates to the models to assess their impact, if any, on the intervention outcome effects. Some of the covariates to potentially be considered at baseline include biological sex, age, BMI, race, ethnicity, education, income, Adverse Childhood Experiences (ACEs), trial expectations/reasons for joining the trial, marital status, work status, type of diabetes, number of years with diagnosed diabetes and whether insulin-treated or non-insulin treated. We will also explore potential effects of diabetes-related medication changes that took place during the trial that could have impacted the outcome measure at-hand (and/or self-reported adherence to prescribed diabetes medications). As many diabetes patients take medications to lower their HbA1c, this will be an important factor to control for during analysis.

We will follow the principle of intention-to-treat for all primary analyses. In other words, we will include the data on each randomized participant in the statistical analyses, regardless of whether that participant was fully engaged in the study (e.g. participants who were randomized and withdrew prior to starting their randomized allocation, participants who remained active in the study but were not fully compliant in attending their randomized allocation study sessions, level of home practice engagement, etc.). Secondary analyses may explore subgroups of subjects with higher engagement and/or compliance with their study sessions (e.g. subjects who attended at least 8 out of the first 10 sessions). We may use the observed data to determine if/how participants who completed the study differed from those who did not. Statistical methods to account for differential dropout will be considered, if applicable.

Method to Assess Potential Mediating Effects
For the primary outcome of hemoglobin A1c, we want to ensure that potential mediators (e.g. stress) are considered so that the effect of the MBSR intervention on the primary outcome is appropriately

estimated. Various measures of stress (and other potential mediators) are collected throughout the study longitudinally using questionnaires and surveys at each of the study visits (Baseline, 2MO, 6MO). Using the generalized linear regression methods presented by VanderWeele (2014), the overall effect on the primary outcome of the change in hemoglobin A1c will be decomposed into 4 components: (1) the controlled direct effect (CDE) due to MBSR intervention, (2) the reference interaction (IRF) between the MBSR intervention and the mediator, (3) the mediated interaction (IMD) between the MBSR intervention and the mediator, and (4) the pure indirect effect (PIE) due to the mediator. Dividing each of these components by the total effect provides the corresponding proportion contributions of these components. These 4 components will provide insight into how much of the total overall effect is: (a) due to neither mediation nor interaction (i.e., CDE), (b) due to interaction (i.e., IRF), (c) due to both mediation and interaction (i.e., IMD), and (d) due to mediation (i.e., PIE). Other potential mediators of the primary outcome will be assessed similarly, and additional exploratory subgroup analyses may be performed to explore these potentially mediating effects whenever necessary. The plan is to use SAS PROC CAUSALMED.

All hypothesis tests will be two-sided and we will invoke a 0.05 two-sided significance level for all primary and secondary statistical analyses. As our analyses are based upon defined hypotheses, we have not included corrections for multiple testing. While the issue of p-value adjustment for multiple testing has long been a topic of discussion in observational epidemiology and clinical trials, it generally is accepted that p-values should not be the sole criterion for assessing relationships. Conclusions will be based on the preponderance of scientific evidence related to each hypothesis, considering point estimates and confidence intervals, as well as statistical significance. Nonetheless, findings with marginal statistical significance will be interpreted cautiously, taking into consideration a type I error. Further, we deem that interim statistical analyses are not necessary for this trial, so we will not pursue such analyses. All analyses will be performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC), R software, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria), or Stata software, version 13 (StataCorp LP, College Station, TX).

9.0 Data and Safety Monitoring Plan

9.1 Periodic evaluation of data

Interim statistical analyses of primary and secondary outcomes are not necessary for this trial and will not be performed.

9.2 Data that are reviewed

Recruitment, enrollment, retention, demographics, subject status, adherence to study intervention, patient-reported safety assessments and Adverse Events data will be reviewed. See Data and Safety Monitoring Plan in Appendix.

9.3 Method of collection of safety information

For this study, we adapted recent recommendations and resources provided by Dr. Willoughby Britton, an external consultant with expertise in the adverse effects of mindfulness-based interventions, and updated the adverse event (AE) collection and reporting methods, and the CRFs for tracking and tabulating adverse events, that we used in our previous NIH-funded mindfulness study. Additionally, Dr. Britton recently updated the National Center for Complementary and Integrative Health (NCCIH) DSMP template v.3.0 to meet CONSORT Harms Criteria, which we used as a guide to update our DSMP (Ioannidis et al., 2004).

Adverse events will be recorded at each study visit (the baseline study visit, follow-up phone call after Class #4, 2-month study visit, and 6-month study visit) and throughout the study whenever subjects or their instructors initiate reporting of an adverse event. Within 24 hours, adverse events in participants assigned to MBSR will be reported via phone or email by Dr. McCown from West Chester University (or other study MBSR instructor e.g. Holly Socolow) to the SME instructors to maintain blinding. Within 24 hours, adverse events in all participants (MBSR and SME) will be reported via phone or email by the SME instructor to the blinded research coordinator and the overall study PI Dr. Raja-Khan at the primary site at Hershey. The SME instructor will communicate adverse events (e.g. requiring a change in MBSR or SME practice recommendations), and other information about MBSR subjects and SME subjects, to the blinded research coordinator and to Dr. Raja-Khan in a manner that does not reveal which instructor the subject reported the adverse event to, or any other information that would reveal the subject's group assignment. To accomplish this, we will minimize the 'discussion' aspect of how the SME instructors report the AE, or any other information about a subject, to the research coordinator because discussion of the report may lead to unblinding/may make it obvious as to which instructor it was reported to if the SME instructor doesn't know much about the encounter. The SME instructor will simply state e.g. "Participant ID 123 has reported <a symptom or potential adverse event or other information worded in a manner that does not reveal the subject's group assignment> to an instructor." The research coordinator will then follow up with the subject via phone for formal AE documentation. If indicated, the research coordinator will complete an Adverse Event form.

All subjects will be followed up to 6 months. Adverse events will be followed for outcome information until resolution or stabilization. Adverse events will also be entered in the REDCap database.

Adverse Event Forms will be completed for each adverse event that a subject experiences (See Data and Safety Monitoring Plan in Appendix). Severity and expectedness will be determined using a specific set of external criteria provided by Dr. Britton who is independent from the study team and does not have a conflict of interest (See Severity Grading Tool and Dr. Britton's List of Previously-Reported Meditation Effects). These external criteria include precise definitions for severity and expectedness. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will also be utilized for AE reporting (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). We will use Dr. Britton's List of Previously-Reported Meditation Effects to determine whether the symptom is an expected effect, and to determine the symptom Domain out of 8 domains including a Diabetes Domain in addition to Dr. Britton's 7 domains (Affective, Cognitive, Conative, Perceptual, Sense of Self, Social, and Somatic). This is in-line with CONSORT harms guidelines as it improves precision and reduces subjectivity around the assessment of severity and expectedness.

Furthermore, the Stress Experience Survey which includes questions about the most common meditation-related symptoms and other stress-related symptoms, will be administered by the research coordinator at the baseline study visit, follow-up phone call after Class #4, 2-month study visit, and 6-month study visit. Additionally to allow for corrective feedback during the MBSR course, subjects will be sent a link from REDCap to complete a Midway Check-in questionnaire after Class #5 so that instructors can adjust mindfulness practice recommendations when indicated based on subjects' responses.

The research coordinator will administer a Hypoglycemia Survey at the baseline study visit, follow-up phone call after Class #4, 2-month study visit, and 6-month study visit. The Hypoglycemia Survey will ask about self-reports of Level 2 hypoglycemia (glucose < 54 mg/dL) and Level 3 hypoglycemia (hypoglycemia requiring the assistance of another person for treatment). Level 2 hypoglycemia will be recorded as an Adverse Event. Level 3 hypoglycemia will be recorded as a Serious Adverse Event (see DSMP).

The Principal Investigator will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, NIH, CRC/CTSI and DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research team.

The Research Coordinator will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, NIH, CRC/CTSI and DSMB of all Unanticipated Problems/Serious Adverse Events (SAEs). See Data and Safety Monitoring Plan in Appendix.

9.4 Frequency of data collection

All data collection will begin immediately upon enrollment. Study accrual, subject retention, subject adherence to intervention sessions, and study safety will be reviewed by the DSMB every 6 months (and more frequently if needed) starting 6 months after randomization of the first cohort. The PHQ-9 will be administered at the baseline study visit, 2-month study visit, and 6-month study visit to screen for depression and suicide. The Stress Experience Survey which includes questions about the most common meditation-related symptoms and other stress-related symptoms, will be administered by the research coordinator at the baseline study visit, follow-up phone call after Class #4, 2-month study visit, and 6-month study visit. Additionally, to allow for corrective feedback during the MBSR course, subjects will be sent a link from REDCap to complete a Midway Check-in questionnaire after Class #5 so that instructors can adjust mindfulness practice recommendations when indicated based on subjects' responses. The research coordinator will also administer a Hypoglycemia Survey at the baseline study visit, follow-up phone call after Class #4, 2-month study visit, and 6-month study visit. See Data and Safety Monitoring Plan in Appendix.

9.5 Individuals reviewing the data

See Data and Safety Monitoring Plan in Appendix.

9.6 Frequency of review of cumulative data

See Data and Safety Monitoring Plan in Appendix.

9.7 Statistical tests

Not applicable

9.8 Suspension of research

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

The PI will include an assessment of futility in the annual progress report to NIH and will consult with the study monitors and the NIH Program Official to assess the impact of significant data loss due to problems in recruitment, retention, or data collection.

10.0 Risks

Risks of Stress Reduction Programs

Meditation-related risks: NCCIH states that meditation is generally safe for healthy people, but that adverse effects have also been reported (NCCIH, 2018). Undesirable side effects and risks of meditation have been

documented in more than 40 scientific reports [for reviews see (Lindahl et al., 2017; Lustyk et al. 2009; Kuijpers et al., 2007; Baer et al, 2019; Britton, 2019; Van Dam et al., 2018)] and are listed in Mindfulness-Based Program Guidelines (Kuyken et al., 2012; Santorelli et al., 2017). More common, less serious side effects that have been reported by individuals within the context of mindfulness-based interventions (MBIs) or who are meditating less than an hour of daily practice include: increased depression, anxiety or panic, re-experiencing of traumatic memories, dissociation, executive dysfunction, headaches/body pain and insomnia (Lindahl et al., 2017; Lomas et al., 2014; Cebolla et al., 2014; Brooker et al., 2013; Johnson et al., 2016; Reynolds et al., 2017; Britton et al., 2010). A few case reports of more serious side effects including mania, psychosis, and suicidality have been reported, mostly in the contexts of intensive retreats (>5 hrs/day) or in conjunction with pre-existing psychopathology (Lindahl et al., 2017; Kuijpers et al., 2007; Kuyken et al., 2012; Yorston, 2001). The frequency of serious adverse effects in the context of MBIs is estimated to be less than 1%, although adequate estimates are not available (Wong et al., 2018). The frequency of non-serious Adverse Events with mild-moderate impairment in functioning is unknown; available estimates range from 1-25% (Baer et al., 2019).

To minimize this risk, we will monitor subjects' levels of distress during the study and use trained instructors who are experienced in detecting when participants of their MBSR class are experiencing increased distress and then providing appropriate corrective feedback e.g. adjustment of MBSR practice, referral to a mental health specialist, etc. Subjects will be monitored for the most common meditation-related symptoms and other stress-related symptoms with the Stress Experience Survey at the baseline study visit, follow-up phone call after Class #4, 2-month study visit, and 6-month study visit. Additionally, subjects will be monitored at each study visit for worsening depressive symptoms and suicidal thinking using the Patient Health Questionnaire-9 (PHQ-9). Subjects with suicidal ideation will be referred to one of the following appropriate resources for immediate evaluation:

1. Dr. Dahlia Mukherjee (cell 775-351-9927)
2. Dr. Erika Saunders (pager 2292, cell 717-514-3818)
3. Psychiatric consult

Additional resources for meditation-related adverse effects, including dissociation:

- The study MBSR instructors Holly Socolow and Dr. Donald McCown
- Co-Investigators Dr. Jeffery Greeson and Dr. Elizabeth Hoge
- External consultant Dr. Willoughby Britton

Risks of Exercise

During the study treatment sessions subjects may be asked to perform gentle stretching and other light exercises. There are risks inherent to any exercise program. Such risks include, but are not limited to, risk of slip, trip, fall, and bodily injury. The instructors will work with subjects to minimize these risks.

Risks of Hypoglycemia

The Oxford Mindfulness Centre's "Mindfulness-Based Cognitive Therapy (MBCT) Exclusion Criteria Explained" document in the Meditation Safety Toolbox (https://www.brown.edu/research/labs/britton/resources/meditation-safety-toolbox) lists insulin-treated diabetes as a potential issue that they have found can limit or prevent people from benefitting from their public MBCT courses. According to this document, which is addressed to potential participants, for people with insulin-dependent diabetes: "During periods of meditation the body may become relaxed and for some people, over time, meditation reduces stress. This may in turn have an effect on blood glucose and insulin requirements and may potentially result in a need for adjustments to pattern of insulin administration and dosage. Please let your GP or other healthcare professional know that you are doing the course and discuss this possibility with them."

People with diabetes are at risk for hypoglycemia when they start any new exercise or lifestyle program, especially if they are on insulin or insulin secretagogues. This does not mean that exercise and lifestyle programs are contraindicated in diabetes. On the contrary, due to their numerous benefits, exercise and lifestyle programs are strongly encouraged in people with diabetes, with monitoring of blood glucose levels and adjustment of

medication doses as needed. Therefore, diabetes should not be considered an absolute contraindication to mindfulness.

To minimize the risk of hypoglycemia, as we do with any exercise or lifestyle program, we will inform subjects that if they are on certain diabetes medications, such as insulin or a sulfonylurea, they may be at risk for hypoglycemia (blood glucose less than 70 mg/dL) during or after the stress reduction sessions or home practice due to the effects of stress reduction or exercise on blood glucose. Regardless of the medications subjects are on, they will be advised to check their blood glucose before and after each stress reduction session and home practice (and during long or intense stress reduction sessions or home practice). They will be advised to carry the following items with them at all times, including at their study visits and stress reduction sessions: their glucometer, testing supplies, and carbohydrate-rich foods such as juice, hard candies or glucose tablets to treat hypoglycemia if it occurs. If they have glucagon, they will be advised to also carry it with them at all times. They will be provided written guidelines about how to monitor for, treat, and prevent hypoglycemia. They will be advised to ask their physician for instructions on adjusting their diabetes medications, if needed, when participating in the stress reduction sessions, or doing home practice.

Subjects will be advised of possible signs and symptoms of hypoglycemia which may include:

- Headache
- Nervousness or feeling anxious
- Weakness
- Dizziness or light-headedness
- Confusion
- Sleepiness
- Irritability
- Hunger
- Fast heartbeat
- Sweating
- Feeling shaky or jittery
- Loss of consciousness if left untreated

In a joint position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes, the International Hypoglycaemia Study Group recommends the following proposed glucose cutoffs when reporting the frequency of hypoglycemia in clinical trials of glucose-lowering drugs, as well as of non-pharmacological interventions, for the treatment of diabetes mellitus (International Hypoglycemia Study Group, 2017):

Level 1: A glucose alert value of 70 mg/dL or less. This need not be reported routinely in clinical studies, although this would depend on the purpose of the study.

Level 2: A glucose of < 54 mg/dL is sufficiently low to indicate serious, clinically important hypoglycemia

Level 3: Severe hypoglycemia, as defined by the ADA denotes severe cognitive impairment requiring the assistance of another person for treatment (Workgroup on Hypoglycemia, ADA, 2005; Seaquist et al., 2013).

Therefore, the research coordinator will administer a Hypoglycemia Survey at the baseline study visit, follow-up phone call after Class #4, 2-month study visit, and 6-month study visit. The Hypoglycemia Survey will ask about self-reports of Level 2 and Level 3 hypoglycemia. Level 2 hypoglycemia will be recorded as an Adverse Event. Level 3 hypoglycemia will be recorded as a Serious Adverse Event (see DSMP).

Subjects will be advised to have 911 called if they ever have severe hypoglycemia, which is when they are having symptoms that are keeping them from being able to treat hypoglycemia themselves and they require the assistance of another person to treat their hypoglycemia. They will be advised to contact their physician and the study team if they ever have a glucose less than 54 mg/dL or hypoglycemia requiring the assistance of another person to treat. They will be advised to contact their physician if their blood glucose level ever drops below their goal during the night or upon awakening, or if their blood glucose level frequently drops below their goal at other times of the day.

Risks of Fasting

The risks of fasting include feeling light-headed, dizzy or faint. If subjects are on certain diabetes medications, such as insulin or a sulfonylurea, they may be at risk for hypoglycemia while fasting for the study visits, and their

medications may need to be adjusted when they are fasting. They will be advised to ask their physician for instructions on adjusting their diabetes medications, if needed, while fasting.

Risks of Venipuncture

The discomfort associated with removing blood by venipuncture (by needle from a vein) is a slight pinch or pin prick when the sterile needle enters the skin. The risks include mild discomfort and/or a black and blue mark at the site of puncture. Less common risks include a small blood clot, infection or bleeding at the puncture site, and on rare occasions fainting during the procedure. To minimize discomfort from blood sampling, the amount of blood we will remove will be 60 mL (4 tablespoons) or less.

Risks of Randomization

Subjects will be randomly assigned to one of two different stress reduction programs. The study stress reduction program a subject receives may prove to be less effective or to have more side effects than the other study stress reduction program or other available treatments.

Risks of Loss of Confidentiality

There is a risk of loss of confidentiality if subjects' information or their identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening. The confidentiality of subjects' electronic data created by the subject or by the researchers will be maintained as required by applicable law and to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed.

During the study stress reduction sessions, all participants will be instructed to keep all conversations occurring during the sessions completely confidential. Furthermore, subjects will be reassured that they are not required to answer any questions or reveal any information that they do not want to.

Risks of Questionnaires

Subjects may get tired or bored when we are asking them questions or they are completing questionnaires or responding to Experience Sampling Surveys. Subjects will be reassured that they do not have to answer any question they do not want to answer.

The potential psychological risks of completing the BRFSS ACE and CTQ questionnaires are minimal. As is recommended, we preface these questionnaires by informing subjects beforehand that some of the questions may make them feel uncomfortable, and they are free to skip any of the questions they do not want to answer. These types of questionnaires are commonly completed by study participants, and our study personnel will be able to appropriately respond to any stress responses. If patients feel uncomfortable, we will help them process through it so that they are ok by the end of the study visit.

Risks of High Blood Glucose

The study stress reduction programs are not expected to increase subjects' blood glucose levels. However, it is possible that in the process of collecting subjects' glucose data from their glucometers, CGM and other diabetes devices, we become aware of hyperglycemia (increased blood glucose level). Subjects will be provided written guidelines about how to monitor for and prevent hyperglycemia. Subjects will be advised to contact their physician if their blood glucose levels are persistently elevated above their goal. In the event of severe hyperglycemia (blood glucose level persistently over 350 mg/dL), subjects will be referred to the Emergency Department at Milton S. Hershey Medical Center, or a local Emergency Department, for immediate evaluation.

Unforeseen Risks

There may be unknown risks or risks that we cannot predict associated with being in this research. It is possible that the study procedures could detect a possible unknown medical problem that is unrelated to the purpose of this study. If the research procedures uncover findings that may be important for subjects to know about, such as the possibility of a previously unknown medical condition, a member of the study team will contact the subject to

find out if they would like to learn more. These findings may require additional testing or treatment. The cost of any additional tests or related treatment will be the subject's responsibility.

The Data and Safety Monitoring Board (DMSB), an independent group of experts, will be reviewing the information from this research throughout the study. If any important new information about the study develops that may affect subjects' health, welfare, or willingness to stay on the study, the PI will inform the subjects, and the subjects may be asked to sign another consent form at that time.

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

Subjects in the MBSR group may benefit from increased awareness of their feelings and thoughts about their diabetes, reduced subjective stress, improved quality of life and overall well-being, and possibly better blood glucose control and reduced risk for diabetes complications. Subjects in the SME group may benefit from health education about general stress management, nutrition, and exercise. Although all of these benefits are possible, they cannot be guaranteed. Most importantly, the potential benefits of MBSR and the risks of continuing to ignore stress in patients with uncontrolled diabetes outweigh the minimal risks associated with doing the proposed study.

11.2 Potential Benefits to Others

The results of this research may guide the future treatment of diabetes. The knowledge gained from the proposed study may help researchers to develop effective comprehensive treatment programs for patients with diabetes that address both the mind and the body to reduce stress, improve glucose control and other key health outcomes, and optimize overall health and wellbeing in patients with diabetes.

12.0 Sharing Results with Subjects

Subjects will receive the results of their hemoglobin A1c levels checked during the study. Hemoglobin A1c is a measure of average glucose levels over the past 3 months and is widely used as an assessment of glucose control in patients with diabetes.

13.0 Subject Payment and/or Travel Reimbursements

Subjects will be compensated $25 for completing the screening visit, $35 for completing the baseline study visit, $50 for completing the 2-month study visit and, $70 for completing the 6-month study visit.

Additionally, subjects will be compensated a total of up to $105 for completing 14 MBSR or SME sessions (Orientation, Class #1 to 8, Retreat, and Booster sessions #1 to 4) as $5 per session for the first 5 sessions they attend, $8 per session for the next 5 sessions they attend, and $10 per session for the next 4 sessions they attend. The money for completing the sessions will be given to the subjects at the 2-month study visit and 6-month study visit.

Finally, subjects will be compensated a total of $15 if they respond to at least 70% of the Experience Sampling Surveys (both Stress and Cravings and Daily Diary) by their 2-month study visit.

The total amount subjects will receive for participation in this research study is up to $300. If subjects do not complete the study for any reason, they will be paid for the study visits and stress reduction sessions they have completed.

14.0 Economic Burden to Subjects

14.1 Costs

The costs to subjects include their time, and travel if study visits are conducted in-person.

14.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

15.0 Resources Available

15.1 Facilities and locations

Study visits and procedures will be carried out at the Clinical Research Center at the Penn State Health Hershey Medical Center when open and available, or remotely via PSHTeams. The MBSR and SME intervention sessions will be delivered remotely via PSU Zoom by instructors at Penn State University and Westchester University of Pennsylvania.

15.2 Feasibility of recruiting the required number of subjects

The study team has access to more than 29,000 patients with diabetes who are potential subjects for the study (7,385 through Endocrinology clinics, 8,784 through Internal Medicine clinics, and 13,032 through Family Medicine clinics). Only 1% of these potential subjects (290 subjects) need to be recruited. The PI Dr. Raja-Khan has a proven track record of randomizing 86 women with overweight and obesity, including women with diabetes, prediabetes and polycystic ovary syndrome in her previous mindfulness study. Additionally, as an endocrinologist Dr. Raja-Khan has a clinical practice with many patients with uncontrolled diabetes. We have submitted an Enterprise Information Management data request using TriNetx, which has identified over 5,000 patients that meet our study criteria. Finally, our team includes Dr. Legro who has expertise in the conduct of numerous multicenter clinical trials.

15.3 PI Time devoted to conducting the research

Through the Penn State College of Medicine Physician-Scientist Effort Matching Program, Dr. Raja-Khan will have a total of 50% effort to devote to this research (25% effort will be provided by the NIH for this R01 and 25% effort will be matched by the College of Medicine and the Department of Medicine). Dr. Raja-Khan is also the PI of a Department of Medicine Innovation Pilot Award, but this is a much smaller pilot study of only 34 subjects. Dr. Raja-Khan is in clinic one half-day per week. Therefore, Dr. Raja-Khan will have sufficient time to devote to conducting and completing this research.

15.4 Availability of medical or psychological resources

If applicable, medical or psychological resources will be provided at the Penn State Health Hershey Medical Center.

15.5 Process for informing Study Team

The project will be governed by a steering committee (SC) with Dr. Raja-Khan as Chair and Dr. Legro as Vice Chair (they will be responsible for the recruitment, management, and safety of subjects in the trial along with co-investigators). The SC will consist of all the funded investigators and research coordinator and meet weekly as part of their regularly scheduled research meeting. These weekly meetings provide a platform for study updates, training and valuable information for the ongoing conduct of the trial.

16.0 Other Approvals

16.1 Other Approvals from External Entities

A Reliance Agreement with West Chester University of Pennsylvania will be obtained prior to engaging Dr. McCown to teach MBSR in the research study.

16.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – **Penn State** Health **only** – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of "HRP-902 - Human Tissue For Research Form" in CATS IRB.

☐ Animal Care and Use – **All campuses** – Human research involves animals and humans or the use of human tissues in animals

☒ Biosafety – **All campuses** – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – **Penn State Health only** – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes but are no longer needed for clinical use. Upload a copy of "HRP-901 - Human Body Fluids for Research Form" in CATS IRB.

☒ Clinical Research Center (CRC) Advisory Committee – **All campuses** – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – **All campuses** – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – **Penn State Health only** – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of "HRP-903 - Radiation Review Form" in CATS IRB.

☐ IND/IDE Audit – **All campuses** – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☐ Scientific Review – **Penn State Health only** – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Health Cancer Institute (PSCI) Protocol Review Committee or the PSCI Disease Team is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website.

17.0 Multi-Site Study

17.1 Other sites

West Chester University of Pennsylvania (West Chester, PA)

Site PI: Donald McCown, PhD, MAMS, MSS, LSW
Associate Professor, Health
Director, Center for Contemplative Studies Coordinator, Graduate Certificates in Applied Mindfulness & Integrative Health Coordinator, Undergraduate Minor in Contemplative Studies
West Chester University
700 S. Church Street
Ehinger Office Annex, rm 102
West Chester, PA 19383
C: 215.913.8866
Email: DMcCown@wcupa.edu

Qualifications: Dr. McCown is an Associate Professor of health, director of the minor in contemplative studies, and director of the center for contemplative studies at West Chester University of Pennsylvania. He holds a Master of Applied Meditation Studies degree from the Won Institute of Graduate Studies, a Master of Social Service from Bryn Mawr College, and a PhD in Social Science from Tilburg University. He trained as an MBSR teacher through the Center for Mindfulness at University of Massachusetts and at Thomas Jefferson University. His primary research interests include the pedagogy of mindfulness in clinical applications and higher education, applications of complementary and integrative medicine in the community, and the contemplative dimensions of the health humanities. He is author of The Ethical Space of Mindfulness in Clinical Practice, primary author of Teaching Mindfulness: A Practical Guide for Clinicians and Educators, New World Mindfulness: From the Founding Fathers, Emerson, and Thoreau to your Personal Practice, and primary editor of Resources for Teaching Mindfulness: An International Handbook.

IRB: Due to the NIH Single IRB Mandate, Penn State will serve as the single IRB and review the study at each site.

17.2 Communication Plans

The overall study PI Dr. Raja-Khan will maintain regular communication with the other sites through remote videoconferencing meetings with West Chester University and University Park every 2 weeks. Dr. McCown at West Chester University will attend these meetings, where Dr. Raja-Khan will update the other sites with the most current version of the protocol and consent document, and ensure that all modifications have been communicated to the sites. Any problems with the research, interim results and closure of the study will also be discussed during these meetings. Due to the NIH Single IRB Mandate, Penn State will serve as the single IRB and review the study at each site.

17.3 Data Submission and Security Plan

At the end of each MBSR and SME session, unblinded research team members will record study participant attendance in REDCap. Attendance will be recorded in REDCap in a way that does not reveal group assignments to blinded research team members. All sites will safeguard data as required by Penn State IRB information security policies.

17.4 Subject Enrollment

Not applicable. Subject enrollment and randomization will not take place at West Chester University. Subject enrollment will only take place at the primary site at Hershey. Randomization will be performed by the SME instructors as they are unblinded. Dr. McCown at West Chester University (or other study

MBSR instructor e.g. Holly Socolow) will teach MBSR to study participants randomized to MBSR via remote videoconferencing (PSU Zoom). The SME instructors will teach SME to study participants randomized to SME via remote videoconferencing (PSUZoom).

17.5 Reporting of Adverse Events and New Information

Within 24 hours, adverse events in participants assigned to MBSR will be reported via phone or email by Dr. McCown from West Chester University (or other study MBSR instructor e.g. Holly Socolow) to the SME instructors to maintain blinding. Within 24 hours, adverse events in all participants (MBSR and SME) will be reported via phone or email by the SME instructor to the blinded research coordinator and the overall study PI Dr. Raja-Khan at the primary site at Hershey.

The SME instructor will communicate adverse events (e.g. requiring a change in MBSR or SME practice recommendations), and other information about MBSR subjects and SME subjects, to the blinded research coordinator and to Dr. Raja-Khan in a manner that does not reveal which instructor the subject reported the adverse event to, or any other information that would reveal the subject's group assignment. To accomplish this, we will minimize the 'discussion' aspect of how the SME instructors report adverse events, or any other information about a subject, to the research coordinator because discussion of the report may lead to unblinding/may make it obvious as to which instructor it was reported to if the SME instructor doesn't know much about the encounter. The SME instructor will simply state e.g. "Participant ID 123 has reported <a symptom or potential adverse event or other information worded in a manner that does not reveal the subject's group assignment> to an instructor." The research coordinator will then follow up with the subject via phone for formal adverse event documentation. If indicated, the research coordinator will complete an Adverse Event form.

17.6 Audit and Monitoring Plans

We will hold weekly team meetings and biweekly whole study group meetings to ensure all local site investigators conduct the study appropriately. The research coordinator will conduct random monthly audits of study materials at each site to ensure compliance.

18.0 Adverse Event Reporting

18.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.0 Study Monitoring, Auditing and Inspecting

19.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

20.0 Future Undetermined Research: Data and Specimen Banking

20.1 Data and/or specimens being stored

For participants who provide written consent to bio-banking, excess specimens not used in this study will be placed in a biorepository for future research with related health information. Bio-banking will be completed by the Penn State Institute for Personalized Medicine (IPM) and will be linked to participant medical/demographic data through a unique identification number assigned by **The Penn State Personalized Research for Innovation, Discovery, and Education (PRIDE) Program** (PRAMS00040532). Medical and demographic data collected for the currently proposed study will be stored by the IPM per the PRIDE protocol for future use with bio-banked samples. Specimens within the IPM will be labeled with a second layer Study ID.

All samples collected prior to 8/1/2021 will be under the direction of the PRIDE protocol. The samples that are collected after 8/1/2021 will be stored in the IPM, but the samples cannot be released to other investigators using the PRIDE Protocol unless the participant signs a PRIDE Consent.

20.2 Location of storage

Banked specimens will be stored on the PS HMC campus in C2706.

20.3 Duration of storage

Specimens and data will be stored indefinitely.

20.4 Access to data and/or specimens

Access to specimens collected under the current study will be limited to the PI and select members of the IPM staff.

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22.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form

Data and Safety Monitoring Plan (DSMP) – v.04/29/2022

I. Study Identification Information

A. **NIH Study Number—** 5R01DK119379-03
B. **NIH Study Title—** Randomized Controlled Trial of a Six-Month Mindfulness-Based Intervention for Diabetes
C. **Name of Principal Investigator (PI)—** Nazia T. Raja-Khan, M.D., M.S.

II. Study Overview

A. **Brief Description of the Purpose of the Study**— The overall goal of this project is to compare the effectiveness of a six-month Mindfulness-based stress reduction (MBSR) intervention versus stress management education (SME) in improving glucose control and other important outcomes in patients with uncontrolled diabetes (HbA1c ≥7.5%).

B. **Adherence Statement—** The Data Safety Monitoring Board Chair will carry out this Data Safety Monitoring Plan (DSMP) independent of the study and in adherence to the protocol approved by the Penn State Hershey IRB.

Dr. Willoughby Britton's updates to the National Center for Complementary and Integrative Health (NCCIH) DSMP template v.3.0 to meet CONSORT Harms Criteria were adapted in this DSMP (Ioannidis et al., 2004).

III. Confidentiality

A. Protection of Subject Privacy

During this study, all of the materials (e.g., biometric data, surveys, biologic specimens) collected are for research purposes only, and data will be kept in strict confidence. No information will be given to anyone without permission from the subject. Confidentiality will be ensured by use of identification codes. All data, whether generated in the laboratory or at the study visit, will be identified with an identification code unique to the subject.

B. Database Protection

The database will be secured with password protection. The informatics manager 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. Source documents including all paper and electronic records for all enrolled subjects, i.e., case report forms, laboratory reports, subject study binders, etc. will also be secured. Electronic source documents will be secured with password protection. Paper source documents will be kept in locked files in the Investigators' academic office.

As part of the Penn State Clinical and Translational Science Institute (CTSI), Penn State is a member of the Research Electronic Data Capture (REDCap) Consortium. Study data, including questionnaires and lab data, will be managed using REDCap which is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g., for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The data management system will allow research staff to register participants, generate participant visit schedules, enter data, edit entry errors, and determine entry status of participant forms. Database access for REDCap is granted on a study-by-study basis. At the start of the trial when the database is created all research personnel will be given defined user roles and assigned a unique username and password. Using the REDCap database management application, each new participant will be registered into the trial

registry. The registry will assign a unique identification (ID) number to the participant that links his/her data across multiple tables. REDCap allows for data type and range checks at the point of data entry and provides clear alerts for valid entry ranges or types. In addition to the range checks built into REDCap at the point of data entry, extreme outliers and missing data for our primary and secondary outcomes as well as baseline demographic and clinical characteristics will be queried by the biostatisticians prior to data analysis to ensure completeness and accuracy of our reported data. REDCap was developed by a multi-institutional consortium, which includes Penn State, and was initiated at Vanderbilt University. The database is hosted at the Penn State Health Hershey Medical Center and College of Medicine data center, which will be used as a central location for data processing and management.

The research coordinator, who is blinded to group assignment, will enter the subject data into the REDCap database. The SME instructors, who are not involved in the collection or analysis of outcomes, will randomize subjects using the REDCap randomization module. The REDCap randomization module will be set up so that only the SME instructor or other unblinded research staff members who need to access randomization information will have role rights and exporting rights to ensure blinding.

C. **Confidentiality During Adverse Event (AE) Reporting**

AE reports and annual summaries will not include subject or group-identifiable material unless requested by the DSMB due to safety concerns. Each report will only include the identification code.

IV. Adverse Event Information

A. **Definition**

An adverse event (AE) is any untoward medical occurrence in a subject temporally associated with participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these.

A Serious Adverse Event (SAE) is any AE that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- Important medical event based upon appropriate medical judgment

B. **Classification of AE Severity**

AEs will be labeled according to severity, which is based on their impact on the patient. Severity grade will be determined as 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very Severe, or 5 = Death according to the Common Terminology Criteria for Adverse Events (CTCAE) and other sources for grading the severity of adverse events. Severity seriousness will be determined as Serious or Not Serious. Seriousness, which requires a different reporting procedure is defined according to the Office for Human Research Protections, Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (Linden, 2013; OHRP, 2007; NCI, 2017). These classifications will be determined using a specific set of external criteria with precise definitions provided by Dr. Willoughby Britton who is independent from the study team and does not have a conflict of interest (See Severity Grading Tool in Appendix C1). The descriptions and grading scales

found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will also be utilized for AE reporting (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

C. **AE Attribution Scale (Relatedness)**

To assess the relationship of an event to the study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

AEs will be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled as "0 = Not related, 1 = Unlikely related, 2 = Possibly related, 3 = Probably related, or 4 = Definitely related. Additionally, we will use Dr. Britton's List of Previously-Reported Meditation Effects (See Appendix C2) to determine whether the symptom is an expected effect, and to determine the symptom Domain out of 8 domains including a Diabetes Domain (See Appendix D) in addition to Dr. Britton's 7 domains (Affective, Cognitive, Conative, Perceptual, Sense of Self, Social, and Somatic).

Relatedness to treatment will be assessed according to 8 causality and relatedness criteria that regulatory agencies such as the World Health Organization (WHO), the Federal Drug Administration (FDA), and the National Institutes of Health (NIH) use to make health policy decisions (NIH, 2016; Agbabiaka et al., 2008; Turner, 1984; WHO, 2016). These criteria are designed to assess treatment-relatedness in individual cases in the absence of prospective or epidemiological (base rate) data. The 8 standard causality/relatedness criteria are 1) prior published reports, and expert judgment, 2) subjective attribution, 3) temporal proximity (challenge), or exacerbation, 4) consistency, 5) dose-response gradient 6) de-challenge, 7) re-challenge, 8) specificity, (Turner, 1984; Naranjo, 1986; Naranjo, 1982; Naranjo, 1981; Hill, 1965; Hill, 2015; Gallagher et al., 2011; Theophile et al., 2010).

The Relatedness Criteria Definitions table below provides detailed definitions for assessing relatedness in individual cases.

Relatedness Criteria Definitions Table	
1. Previous Reports/known effects and expert judgment	Symptom has been previously reported in association with meditation or judged to be caused by meditation by experts (meditation teachers/clinicians)
2. Subjective attribution	Participant thinks symptom was caused by meditation
3. Temporal proximity OR Exacerbation	Symptom occurred for the first time OR pre-existing symptoms got worse during/following treatment
4. Consistency	More than one occasion following meditation
5. Dose/gradient	Symptom was worse with higher dose of treatment
6. De-challenge	Decreased when stopped meditation
7. Re-challenge	Re-appeared or increased when meditation restarted

8. Specificity	Presence of plausible alternative cause: Something other than meditation (medical illness, life event, substances) could account for symptom (meditation played no causal role).

D. **Expected Risks**

Expected risks to the subject are as follows:

- Inserting a needle for blood sampling can be associated with some discomfort and bruising, and very rarely with inflammation and infection of the arm veins.
- Loss of subject confidentiality.

These risks are considered to be minimal and are addressed in the protocol and consent form.

To minimize discomfort from blood sampling, we will require only a minimal amount of blood ~ 60 ml.

All questionnaires and subject data forms will be coded with unique identification numbers to protect subject confidentiality. To reduce the risk of breaching confidentiality, subjects will be instructed to keep all conversations occurring during the sessions completely confidential. Furthermore, subjects will be reassured that they are not required to answer any questions or reveal any information that they do not want to.

Meditation-related risks: NCCIH states that meditation is generally safe for healthy people, but that adverse effects have also been reported (NCCIH, 2018). Undesirable side effects and risks of meditation have been documented in more than 40 scientific reports [for reviews see (Lindahl et al., 2017; Lustyk et al. 2009; Kuijpers et al., 2007; Baer et al, 2019; Britton, 2019; Van Dam et al., 2018)] and are listed in Mindfulness-Based Program Guidelines (Kuyken et al., 2012; Santorelli et al., 2017). More common, less serious side effects that have been reported by individuals within the context of mindfulness-based interventions (MBIs) or who are meditating less than an hour of daily practice include: increased depression, anxiety or panic, re-experiencing of traumatic memories, dissociation, executive dysfunction, headaches/body pain and insomnia (Lindahl et al., 2017; Lomas et al., 2014; Cebolla et al., 2014; Brooker et al., 2013; Johnson et al., 2016; Reynolds et al., 2017; Britton et al., 2010). A few case reports of more serious side effects including mania, psychosis, and suicidality have been reported, mostly in the contexts of intensive retreats (>5 hrs/day) or in conjunction with pre-existing psychopathology (Lindahl et al., 2017; Kuijpers et al., 2007; Kuyken et al., 2012; Yorston, 2001). The frequency of serious adverse effects in the context of MBIs is estimated to be less than 1%, although adequate estimates are not available (Wong et al., 2018). The frequency of non-serious Adverse Events with mild-moderate impairment in functioning is unknown; available estimates range from 1-25% (Baer et al., 2019).

Because of these risks, subjects will be monitored at frequent intervals throughout the study for expected and unexpected Adverse Events. Risks will be further minimized by employing trained instructors who are experienced in detecting when participants of their MBSR class are experiencing increased distress and then providing appropriate corrective feedback e.g. adjustment of MBSR practice, referral to a mental health specialist, etc.

The Stress Experience Survey will be administered by the research coordinator at the baseline study visit, follow-up phone call after Class #4, 2-month study visit, and 6-month study visit. This includes questions about the most common meditation-related symptoms (items 1 to 10) and a question about other stress-related symptoms. This survey was adapted from Dr. Willoughby Britton's MBP-Specific Adverse Effects Survey (Britton_Version9.18.19), which represents the 10 most common meditation-related symptoms from the Varieties of Contemplative Experience Phenomenology Codebook (Lindahl et al., 2017), as replicated in an NIH-funded mindfulness-based intervention clinical trial (Britton, in prep).

Additionally to allow for corrective feedback during MBSR, subjects will be sent a link from REDCap to complete a Midway Check-in questionnaire after Class #5 so that instructors can adjust mindfulness practice recommendations when indicated based on subjects' responses. The study

MBSR instructors have been provided with resources to supplement their teacher training with meditation safety and trauma informed mindfulness, including the Meditation Safety Toolbox (https://www.brown.edu/research/labs/britton/resources/meditation-safety-toolbox) and Trauma-Sensitive Mindfulness (https://davidtreleaven.com/).

At each study visit subjects will be screened for depressive symptoms and suicidal thinking using the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 will be self-administered in REDCap at the screening visit, baseline visit, 2-month visit, and 6-month visit. At every study visit, the blinded research coordinator will review the subjects' responses to the PHQ-9 in REDCap. If any answers are missing, the research coordinator will ask the subject: "Are you sure you meant to skip this question?" If the subject did not mean to skip the question, the research coordinator will be able to go in and enter the subject's response (REDCap will track that the research coordinator entered the response).

If a subject is not comfortable with answering the 9th item of the PHQ-9 at the screening visit, they will be excluded from the study. If a subject refuses to answer the 9th item of the PHQ-9 at any of the subsequent study visits, the subject will be excluded from the study, and the research coordinator will immediately contact one of the below suicidality experts.

Subjects' PHQ-9 scores at each of the study visits will be immediately calculated by REDCap, even if subjects refuse to answer all of the PHQ-9 questions. If a subject's PHQ-9 score at any of the study visits is 10 or greater, they will be recommended to see their PCP for further evaluation. The research coordinator will give the subject an Incidental Findings Letter to share with their PCP. This letter will include the subject's PHQ-9 score. These subjects can still continue in the study as long as they meet the other eligibility criteria.

If a subject scores 1 or greater on the 9th item of PHQ-9, a trained research coordinator will interview the subject using the modified P4 Screener to assess suicide risk (Dube et al., 2010). If the subject answers Somewhat Likely or Very Likely to the modified P4 Screener question which asks "How likely do you think it is that you will act on these thoughts about hurting yourself or ending your life some time over the next month?", they are considered higher risk and will not be eligible for the study. For these higher risk subjects, the research coordinator will immediately contact one of the following appropriate suicidality experts, who will immediately evaluate the subject for suicidality and determine if the subject needs to be escorted to the Emergency Department because they have an active suicidal plan in the immediate future:

1. Dr. Dahlia Mukherjee (cell 775-351-9927)
2. Dr. Erika Saunders (pager 2292, cell 717-514-3818)
3. Psychiatric consult

If on the modified P4 Screener, the subject answers Not at all Likely to "How likely do you think it is that you will act on these thoughts about hurting yourself or ending your life some time over the next month?" and they answer No to "Is there anything that would prevent or keep you from harming yourself?" the research coordinator will ask "You said 'Not at all Likely' to Q5. What is stopping you from acting on harming yourself?" If the subject provides a response to what is stopping them from acting on harming themself, they can continue in the study as long as they meet the other eligibility criteria. If the subject cannot provide a response to what is stopping them from acting on harming themself, the subject will be considered higher risk and excluded from the study, and the research coordinator will immediately contact one of the above suicidality experts.

If the subject refuses to answer any of the modified P4 Screener questions at any of the study visits, they will be excluded, and the research coordinator will immediately contact one of the above suicidality experts.

The Oxford Mindfulness Centre's "Mindfulness-Based Cognitive Therapy (MBCT) Exclusion Criteria Explained" document in the Meditation Safety Toolbox (https://www.brown.edu/research/labs/britton/resources/meditation-safety-toolbox) lists insulin-treated diabetes as a potential issue that they have found can limit or prevent people from benefitting from their public MBCT courses. According to this document, which is addressed to potential participants, for people with insulin-dependent diabetes: "During periods of meditation the body may become relaxed and for some people, over time, meditation reduces stress. This may in turn have an effect on blood glucose and insulin requirements and may potentially result in a need for adjustments to pattern of

insulin administration and dosage. Please let your GP or other healthcare professional know that you are doing the course and discuss this possibility with them."

People with diabetes are at risk for hypoglycemia when they start any new exercise or lifestyle program, especially if they are on insulin or insulin secretagogues. This does not mean that exercise and lifestyle programs are contraindicated in diabetes. On the contrary, due to their numerous benefits, exercise and lifestyle programs are strongly encouraged in people with diabetes, with monitoring of blood glucose levels and adjustment of medication doses as needed. Therefore, diabetes should not be considered an absolute contraindication to mindfulness.

To minimize the risk of hypoglycemia, as we do with any exercise or lifestyle program, we will inform subjects that if they are on certain diabetes medications, such as insulin or a sulfonylurea, they may be at risk for hypoglycemia (blood glucose less than 70 mg/dL) during or after the stress reduction sessions or home practice due to the effects of stress reduction or exercise on blood glucose. Regardless of the medications subjects are on, they will be advised to check their blood glucose before and after each stress reduction session and home practice (and during long or intense stress reduction sessions or home practice). They will be advised to carry the following items with them at all times, including at their study visits and stress reduction sessions: their glucometer, testing supplies, and carbohydrate-rich foods such as juice, hard candies or glucose tablets to treat hypoglycemia if it occurs. If they have a glucagon, they will be advised to also carry it with them at all times. They will be provided written guidelines about how to monitor for, treat, and prevent hypoglycemia. They will be advised to ask their physician for instructions on adjusting their diabetes medications, if needed, when participating in the stress reduction sessions, or doing home practice.

In a joint position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes, the International Hypoglycaemia Study Group recommends the following proposed glucose cutoffs when reporting the frequency of hypoglycemia in clinical trials of glucose-lowering drugs, as well as of non-pharmacological interventions, for the treatment of diabetes mellitus (International Hypoglycemia Study Group, 2017):

Level 1: A glucose alert value of 70 mg/dL or less. This need not be reported routinely in clinical studies, although this would depend on the purpose of the study.

Level 2: A glucose of < 54 mg/dL is sufficiently low to indicate serious, clinically important hypoglycemia

Level 3: Severe hypoglycemia, as defined by the ADA denotes severe cognitive impairment requiring the assistance of another person for treatment (Workgroup on Hypoglycemia, ADA, 2005; Seaquist et al., 2013).

Therefore, the research coordinator will administer a Hypoglycemia Survey at the baseline study visit, follow-up phone call after Class #4, 2-month study visit, and 6-month study visit. The Hypoglycemia Survey will ask about self-reports of Level 2 and Level 3 hypoglycemia. Level 2 hypoglycemia will be recorded as an Adverse Event. Level 3 hypoglycemia will be recorded as a Serious Adverse Event.

Subjects will be advised to have 911 called if they ever have severe hypoglycemia, which is when they are having symptoms that are keeping them from being able to treat hypoglycemia themselves and they require the assistance of another person to treat their hypoglycemia. They will be advised to contact their physician and the study team if they ever have a glucose less than 54 mg/dL or hypoglycemia requiring the assistance of another person to treat. They will be advised to contact their physician if their blood glucose level ever drops below their goal during the night or upon awakening, or if their blood glucose level frequently drops below their goal at other times of the day.

In the event of severe hyperglycemia recognized upon downloading subjects' glucometers, subjects will be referred to the Emergency Department at Milton S. Hershey Medical Center, or a local Emergency Department, for immediate evaluation.

E. Adverse Events Reporting and Follow-Up

Adverse events will be recorded at each study visit (the baseline study visit, follow-up phone call after Class #4, 2-month study visit, and 6-month study visit) and throughout the study whenever subjects or their instructors initiate reporting of an adverse event. Within 24 hours, adverse events in participants

assigned to MBSR will be reported via phone or email by Dr. McCown from West Chester University (or other study MBSR instructor e.g. Holly Socolow) to the SME instructors to maintain blinding. Within 24 hours, adverse events in all participants (MBSR and SME) will be reported via phone or email by the SME instructor to the blinded research coordinator and the overall study PI Dr. Raja-Khan at the primary site at Hershey. The SME instructor will communicate adverse events (e.g. requiring a change in MBSR or SME practice recommendations), and other information about MBSR subjects and SME subjects, to the blinded research coordinator and to Dr. Raja-Khan in a manner that does not reveal which instructor the subject reported the adverse event to, or any other information that would reveal the subject's group assignment. To accomplish this, we will minimize the 'discussion' aspect of how the SME instructors report the AE, or any other information about a subject, to the research coordinator because discussion of the report may lead to unblinding/may make it obvious as to which instructor it was reported to if the SME instructor doesn't know much about the encounter. The SME instructor will simply state e.g. "Participant ID 123 has reported <a symptom or potential adverse event or other information worded in a manner that does not reveal the subject's group assignment> to an instructor." The research coordinator will then follow up with the subject via phone for formal AE documentation. If indicated, the research coordinator will complete an Adverse Event form.

All subjects will be followed up to 6 months. Adverse events will be followed for outcome information until resolution or stabilization. Adverse events will also be entered in the REDCap database.

Adverse Events Form

Specifically, the research coordinator will use the Adverse Events Form which includes the CTCAE and accompanying documents (Severity Grading Tool and List of Previously-Reported Meditation Effects in the Appendices, and the Relatedness Criteria Definitions Table above in section IV-C) to provide:

a) A description of the AE/SAE, including the Adverse Event/CTCAE (To document COVID-19 related adverse events, the CTCAE term "Infections and infestations - Other, specify" will be entered. A text box will branch allowing the research coordinator to specify the other condition. The research coordinator will enter "COVID-19" here).
b) MedDRA System Organ Class (SOC)
c) Adverse Event Domain (as categorized in the List of Previously-Reported Meditation Effects in Appendix C2, and in the Diabetes Domain Expected Events in Appendix D).
d) Start and end dates
e) Severity grading (1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very Severe, 5 = Death) based on the CTCAE and the Severity Grading Tool (Appendix C1)
f) Relationship to treatment (using the Relatedness Criteria Definitions Table above in section IV-C and the List of Previously-Reported Meditation Effects in Appendix C2). (0 = Not related, 1 = Unlikely related, 2 = Possibly related, 3 = Probably related, 4 = Definitely related)
g) Action taken (if any) by study team regarding study intervention (0 = None, 1 = Study intervention modification, 2 = Study intervention discontinued)
h) Treatment required for this adverse event (0 = None, 1 = Medication, 2 = Hospitalization, 3 = Other (specify):_____)
i) Outcome of AE (as assessed after 2 weeks or next check-in time point) (1 = Resolved, 2 = Recovered with minor sequelae, 3 = Recovered with major sequelae, 4 = Ongoing/Continuing treatment, 5 = Condition worsening, 6 = Death and 7 = Unknown)
j) Expectedness (1 = Yes, 2 = No) (Refer to List of Previously-Reported Meditation Effects in Appendix C2)
k) Seriousness (1 = Yes, 2 = No) (See Severity Grading Tool for definition of Serious Adverse Event (SAE); use Serious Adverse Events Form if event is Serious)

Serious Adverse Events Form will capture:

a) The date the subject reported the SAE
b) SAE onset date (The date of onset for an SAE is the date the outcome of the AE fulfilled one of the serious criteria).
c) SAE diagnosis date (In some cases this will be the same as the onset date).
d) SAE stop date
e) Description of SAE (CTCAE term) (The research coordinator will enter a symptom, condition/diagnosis (if available), or procedure as the primary event. If a condition/diagnosis has not been identified, the symptom (e.g., chest pain) will be entered, and the event will be updated to the condition/diagnosis when available [e.g., Cardiac Arrest]).
f) Unexpectedness (1 = Yes, 2 = No) (Refer to List of Previously-Reported Meditation Effects in Appendix C2 and Diabetes Domain Expected Events in Appendix D).
g) Age of subject (at time of onset)
h) Sex of subject
i) Brief description of the nature of the SAE (with no personal identifiers)
j) Category of SAE (Death with date of death, Life threatening, Hospitalization-initial or prolonged with admission date and discharge date, Disability/incapacity, Congenital anomaly/birth defect, Required intervention to prevent permanent impairment, or Other:_____)
k) Relatedness (using the Relatedness Criteria Definitions Table above in section IV-C and the List of Previously-Reported Meditation Effects in Appendix C2). (Unrelated [clearly not related to the intervention], Possible [may be related to intervention], Definite [clearly related to intervention]).
l) Whether study intervention was discontinued due to the event? (Yes or No or N/A – event occurred prior to start of study intervention)
m) What medications or other steps were taken to treat the SAE? _____
n) Intervention type (Medication or nutritional supplement, Device, Surgery, Behavioral/lifestyle)
o) List any relevant tests, laboratory data, and history, including preexisting medical conditions:_____
p) Is this the final report? (Yes or No)

E.1 Adverse events will be assessed according to the measures and schedule described in the table below.

Name of measure	Visit # 1 Baseline	Visit #2 Follow-up Phone Call after Class #4 (Middle of 8-wk MBSR/SME)	Visit #3 2-month (End of 8-wk MBSR/SME)	Visit #4 6-month (After Booster session #4/End of Study)
PHQ-9	x		x	x
Stress Experience Survey*	x	x	x	x
Subject initiated (passive monitoring)	Ongoing			
Dropout-reason form	Ongoing, as dropouts occur			
*The Stress Experience Survey, includes questions about the most common meditation-related symptoms and other stress related symptoms. These questions may result in the participant reporting an AE. If this occurs, the AE will be marked as “expected” and compared to Baseline and previous visit responses for proper documentation.				

E.3 Other Measures for Monitoring AEs

E.3.1 **Stress Experience Survey [Adapted from Dr. Britton's Mindfulness-based program-specific adverse effects (MBP-SPEC-AE) survey**]. CONSORT-Harms guidelines (Ioannidis et al., 2004) recommend using standardized and validated scales that assess treatment-specific symptoms, because they have more accurate detection rates than passive monitoring (Stephens et al.,1998) or open-ended queries (Wallin and Sjovall, 1981; Bent et al., 2006) and are low cost, low burden and require no special training to administer.

To accommodate these recommendations, and to create a systematic query of treatment-specific symptoms in all treatment arms, the research coordinator will administer the Stress Experience Survey to specifically query the most common meditation-related side effects (anxiety, depression, dissociation, re-experiencing of traumatic memories etc.) found in 8-week MBIs using patient-reported outcomes measurement information system (PROMIS) or NeuroQol items (or other validated scales if construct is not available). The Stress Experience Survey includes questions about the most common meditation-related symptoms (items 1 to 10), as well a question about other stress-related symptoms. This survey was adapted from Dr. Willoughby Britton's MBP-Specific Adverse Effects Survey (Britton_Version9.18.19), which represents the 10 most common meditation-related symptoms from the Varieties of Contemplative Experience Phenomenology Codebook (Lindahl et al., 2017), as replicated in an NIH-funded mindfulness-based intervention clinical trial (Britton, in prep). Subsequently, the research coordinator will record any item occurring more frequently compared to baseline, or previous visit responses, as an Adverse Event and assess its severity (using the Severity Grading Tool in Appendix C1) and relatedness (using the Relatedness Criteria Definitions Table above in section IV-C). Subjects will be asked to provide further detail (i.e., date of onset, symptomology, circumstance surrounding the event, relatedness to the intervention, etc.) on any AE/SAE reported in the Stress Experience Survey. These details will be used to assess the need for treatment modification, referrals and reporting.

E.3.2 **Hypoglycemia Survey**. The research coordinator will administer a Hypoglycemia Survey at the baseline study visit, follow-up phone call after Class #4, 2-month study visit, and 6-month study visit. The Hypoglycemia Survey will ask about self-reports of Level 2 hypoglycemia (glucose < 54 mg/dL) and Level 3 hypoglycemia (hypoglycemia requiring the assistance of another person for treatment). Level 2 hypoglycemia will be recorded as an Adverse Event. Level 3 hypoglycemia will be recorded as a Serious Adverse Event.

E.3.3 **Subject Initiated (Passive monitoring):** Subjects are encouraged to contact their instructors and/or study staff if any physical or mental health symptoms arise or other study-related problems occur. Subjects may report AEs at any time throughout the study. Events will be evaluated with the Adverse Events Form by study staff.

E.3.4 **Attrition:** Reasons for attrition are also an important source of AEs. The research coordinator will collect attrition information for each dropout from the study, record the dropout date, subjects' responses to Yes/No questions about general reasons for attrition that do not reveal the subjects' group assignment, and whether the dropout is Subject-initiated or Investigator-initiated.

If it is a Subject-initiated dropout or a lost to follow-up, the subject will be e-mailed a link to a REDCap Participant-Completed Attrition Information Survey consisting of one open ended question to elicit feedback about their experience in the study and learn more about their reasons for not continuing in the study. As subjects' responses could reveal group assignment, the research coordinator and other blinded study team members will not have access to subjects' responses to this survey in REDCap.

Investigator-initiated withdrawals: A subject may also be withdrawn from the study and/or intervention by the investigator. In this case, the research coordinator will record the reasons why the investigator withdrew the subject from the study.

To report data on subject status, adherence/attendance at MBSR or SME classes, and attendance at study visits, we will use Tables 3 and 4 in Appendix A.

To report data on Adverse Events and Serious Adverse Events, we will use Tables 6 and 7 in Appendix A.

F. **SAE Reporting**

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Data Safety Monitoring Board, Penn State IRB, Penn State CTSI, and NIH in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NIH Program Officer within 7 days. Other serious and unexpected AEs related to the intervention will be reported to the NIH Program Official within 15 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Data Safety Monitoring Board, Penn State IRB, Penn State CTSI, NIH, and other oversight organizations in accordance with their requirements.
- In the AE summary of the Annual Data and Safety Monitoring Report, the Data Safety Monitoring Board will state that they have reviewed all AE reports.

G. **Expectedness of SAEs**

The Study PI and Independent Data Safety Monitoring Board will be responsible for determining whether an SAE is expected or unexpected. An event is considered expected if it appears on the List of Previously-Reported Meditation Effects in Appendix C2. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

V. Data Quality and Safety Review Plan and Monitoring

A. Data Quality and Management

1) Description of Plan for Data Quality and Management— The PI or study staff will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. All data for this project will be promptly entered into a computerized database. Subjects will enter data directly into REDCap when completing self-administered questionnaires in REDCap. Research staff will enter data from paper forms into REDCap. Data can also be directly entered into REDCap. Subject identifications will be kept separate in locked files and will be destroyed when no longer needed for the project. To minimize errors, measures will be verified prior to data entry and computer verification will be employed during data entry. Data files will be backed up and archived regularly.

2) Frequency of Data Review for this Study— The frequency of data review for this study is summarized in the following Table:

Data type	Frequency of review	Reviewer
Subject accrual (including accrual of minority subjects)	Every 6 months	PI, Data Safety Monitoring Board
Status of all enrolled subjects, as of date of reporting	Every 6 months	PI, Data Safety Monitoring Board
Adherence data regarding study visits and intervention	Every 6 months	PI, Data Safety Monitoring Board
Adverse Events (including out-of-range patient-reported safety assessments)	Every 6 months	PI, Data Safety Monitoring Board
SAEs	Per occurrence	PI, Data Safety Monitoring Board, NIH, IRB, CRC/CTSI

B. Subject Accrual and Compliance

1) Measurement and Reporting of Subject Accrual, Compliance with Inclusion/Exclusion Criteria— Review of the rate of subject accrual and compliance with inclusion/exclusion criteria (verifying that all randomized subjects meet the inclusion/exclusion criteria) will occur every 6 months to ensure that a sufficient number of participants are being enrolled and that they meet eligibility criteria and the targeted ethnic diversity goals outlined in the grant proposal (Targeted/Planned Enrollment Table). If recruitment goals are not being met, recruitment efforts will be targeted to meet any unmet goals. To report data on enrollment and subject demographics, we will use Tables 1 and 2 in Appendix A.

2) Measurement and Reporting of Participant Adherence to Treatment Protocol

   Data on adherence to the treatment protocol will be collected weekly by research staff and reviewed every 6 months by the PI, the study statistician, and the Data Safety Monitoring Board. Adherence of participants will be evaluated by recording attendance at each class. Previous MBSR studies report adherence rates varying from 70-85%. If adherence falls below 75%, which might inhibit the ability of the study to test its primary hypotheses, the PI will suggest a conference call for study investigators to discuss methods for improving adherence.

C. Justification of Sample Size

The goal of this study is to compare the effectiveness of a six-month MBSR intervention versus SME control intervention in improving glucose control and other important outcomes in patients with uncontrolled diabetes. The primary outcome is hemoglobin A1c, which is a measure of average glucose control over the past 3 months. A sample size of 290 subjects (145/group) will provide 80% power to detect a clinically significant 0.5% absolute difference in the mean change in A1c from baseline to month 6, assuming a standard deviation of 0.9%, between the two groups using a two-sided test having a significance level of 0.05. The sample size estimate was based on the intent-to-treat principle and inflated to account for the potential of 15% subject dropout.

D. Stopping Rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

The PI will include an assessment of futility in the annual progress report to NIH and will consult with the study monitors and the NIH Program Official to assess the impact of significant data loss due to problems in recruitment, retention, or data collection.

E. Designation of a Monitoring Committee

The Data Safety Monitoring Board for this study will perform the monitoring outlined in this Data and Safety Monitoring Plan. The independent Data Safety Monitoring Board is well qualified for this role as it is led by a family physician and experienced diabetes researcher, and includes a licensed clinical psychologist and an experienced DSMB statistician. None of the Data Safety Monitoring Board members are involved in this grant as key personnel. Therefore, the Data Safety Monitoring Board will be able to carry out this Data and Safety Monitoring Plan independent of the PI and research team.

F. **Safety Review Plan**

Study accrual, subject retention, subject adherence to intervention sessions, and study safety will be reviewed by the DSMB every 6 months (and more frequently if needed) starting 6 months after randomization of the first study cohort. Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the Data Safety Monitoring Board following each of the reviews. 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 (only blinded information; unblinded information from the open-ended attrition item will not be provided); (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 Data Safety Monitoring Board and will be forwarded to the IRB, NIH, and other applicable recipients who will review the progress of this study on an annual basis.

G. **Study Report Outline for the Data Safety Monitoring Board (Interim or Annual Reports)**

The study team will generate Study Reports for the Data Safety Monitoring Board, and will provide information on the following study parameters: recruitment, enrollment, retention, demographics, subject status, adherence to study intervention, patient-reported safety assessments and AE data. Study Reports for the Data Safety Monitoring Board will not include data on primary or secondary endpoints as there are no interim analyses planned for the study, with the exception of safety outcomes.

Study Report tables will be generated only from aggregate (not by group assignment) baseline and aggregate safety data for the study population. We will use the Study Report Outline in Appendix B.

VI. Informed Consent

Written informed consent will be obtained from each subject at entry into the study. Consent will be obtained by the research coordinator, and not the subject's physician. Potential subjects will be reassured that choosing not to participate will not jeopardize their medical care. Informed consent is obtained by the following process:

1. The subject (If applicable, parent/guardian) will be asked to review the study consent form.
2. The research coordinator will meet with the subject to review the form, to confirm the subject’s understanding of the study, and to answer any questions that the subject might have. The subject will have the opportunity to meet with one of the study investigators, who reviews the eligibility criteria.
3. Once the subject demonstrates understanding of the study and agrees to participate in the study, the consent will be signed in the presence of the research coordinator and a witness.

VII. Reporting Changes in Study Status

During the funding of this study, any action by the IRB or one of the study investigators that results in a temporary or permanent suspension of the study will be reported to the NIH Program Official within 1 business day of notification.

APPENDICES

- **Appendix A: DSMP Study Report Figures/Tables**
- **Appendix B: DSMP Study Report Outline for the Data Safety Monitoring**
- **Appendix C1: Severity Grading Tool**
- **Appendix C2: List of Previously-Reported Meditation Effects**
- **Appendix D: Diabetes Domain Expected Events**

Appendix A

DSMP Study Report Figures/Tables

Figure or Table 1. Quarterly Enrollment and Randomization

A graph or table will depict quarterly enrollment.

Quarter	# Consented/ Enrolled	# Excluded (and reasons for excluding and ineligibility)	# Randomized	# Not Randomized
2020 Q3 (Jul-Sept)				
2021 Q1 (Jan-Mar)				
Total				

Table 2. Demographics

Characteristics	Enrolled Participants	Randomized Participants
Age, years		
Mean (SD)		
Minimum		
Maximum		
Sex, N (%)		
Male		
Female		
Ethnicity, N (%)		
Hispanic or Latino		
Not Hispanic or Latino		
Unknown		
Race, N (%)		
American Indian or Alaska Native		
Asian		
Native Hawaiian or Other Pacific Islander		
Black or African American		
White		
More than one race		
Unknown or Not Reported		
Taking Insulin at Baseline Visit, N (%)	[redacted]	
No	[redacted]	
Yes	[redacted]	
Type of Diabetes, N (%)		
Type 1 Diabetes		
Type 2 Diabetes		
Other		

Table 3. Subject Status and Class Attendance for Randomized Participants

Pt Iden-tifier	Date Enrolled (Consented)	End of Trial Date	Study Status (Active or Inactive)	End of Trial Status (Completed, Withdrew, or Lost to Follow Up)	Total No. of Classes Attended (Max 10)	Total No. of Classes and Boosters Attended (Max 14)	Class Attendance/ Adherence (%)	Class and Booster Attendance /Adherence (%)

% Adherence to Intervention:
Note: % Adherence will be determined:
(1) when the first 10 classes the subject is assigned to ends: (#sessions attended/10)*100
(2) when all 14 of the sessions the subject is assigned to ends: (#sessions attended/14)*100

Table 4. Study Visit Attendance for Randomized Participants

Quarter	Pt Identifier	Date Enrolled (Consented)	End of Trial Date	Study Status (Active or Inactive)	End of Trial Status (Completed, Withdrew, or Lost to Follow Up)	Reached for 4-week Phone Call	Attended 2-month study visit	Attended 6-month study visit

Table 5. Out-of-Range Patient-Reported Safety Assessments in Enrolled Participants

Pt ID	Visit #	9th item of PHQ-9 (Report if ≥1)	Full PHQ-9 (Report if ≥10)	GAD-7 (Report if ≥10)	Higher Risk for Suicide Based on Modified P4 Screener? (Yes, No, or Not Applicable)

Table 6. Adverse Events in Enrolled Participants

Pt Iden -tifier	AE # for Pt	SAE (Yes or No)	Adverse Event/ CTCAE Term	Other Term	CTCAE Grade	Do-main	Start Date	Stop Date	Related to Study Inter-vention	Action Taken	Out-come	Ex-pected

Table 7. Serious Adverse Events (including deaths) in Enrolled Participants*

Pt Identifier	Link to Pt AE #	Date Pt Reported	Onset Date	Dx Date	SAE Stop Date	SAE Category	Related to Study Inter-vention	Age at Onset	Description of Actions and Outcomes (e.g., hospitalization, withdrawn from study)

* Adverse events will be determined to be SAEs based on the Severity Grading Tool (Appendix C1)

SAE Category: Death, Life threatening, Hospitalization-initial or prolonged, Disability/incapacity, Congenital anomaly/birth defect, Required intervention to prevent permanent impairment, or Other:_____

Level 3: Severe hypoglycemia, as defined by the ADA denotes severe cognitive impairment requiring the assistance of another person for treatment, will be considered a SAE (Workgroup on Hypoglycemia, ADA, 2005; Seaquist et al., 2013).

Relatedness: 0 = Not related, 1 = Unlikely related, 2 = Possibly related, 3 = Probably related, or 4 = Definitely related based on the the Relatedness Criteria Definitions Table above in section IV-C and the List of Previously-Reported Meditation Effects (Appendix C2)

Table 7. Serious Adverse Events (including deaths) in Enrolled Participants (Continued)

Pt ID	Link to Pt AE #	Date of Death	Hospital Admission Date	Hospital Discharge Date	SAE Other Catego-ry	Unexpected	Intervention Discontinued due to SAE?	Treat-ment of SAE	Tests, Labs, Medical History, Pre-existing Medical Conditions

Appendix B

DSMP Study Report Outline for the Data Safety Monitoring Board

The study team will prepare a study safety report which will begin with a brief introduction section describing the study status, issues, and procedures that produced the report (e.g., data obtained by specific date). A study description with a current timetable and study schedule will be included. Study data reports will describe enrollment, demographic characteristics and safety assessments. Study Report tables will be generated only from aggregate (not by group assignment) baseline and aggregate safety data for the study population.

Study Report Outline

I. Table of Contents

II. General Information
   a. Quarterly Enrollment and Randomization (see Appendix A, Figure or Table 1)
   b. Demographic Data (see Appendix A, Table 2)
   c. Subject Status (see Appendix A, Table 3)

III. Adherence to protocol
   a. Participant Adherence to MBSR or SME/Class Attendance (see Appendix A, Table 3)
   b. Study Visit Attendance (see Appendix A, Table 4)

IV. Safety Assessment
   a. Out-of-Range Patient-Reported Safety Assessments (see Appendix A, Table 5)
   b. Adverse Events Summary (see Appendix A, Table 6)
   c. SAE Listing including subject deaths (see Appendix A, Table 7)

Appendix C1

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SEVERITY GRADING TOOL

Grade	Description	Detailed Criteria (Linden, 2013; NCI, 2017; OHRP, 2007)
1	**Mild**	• May include transient distress and discomfort, but not enough to cause significant impairment, change in behavior or countermeasures. • Transient or short duration (usu. < than 1 week) • Resolved on its own; no intervention needed • No consequences
2	**Moderate**	• Minimal, local or noninvasive intervention indicated (individual meeting with meditation teacher) • Significant distress or discomfort that involves: • Countermeasures (non-prescription medicine) OR • Change in behavior (cancelling plans, decreasing or discontinuing treatment) OR • Impairment in at least one domain of functioning[a] or activities of daily living (ADL)[b] (25%-50% reduction from usual level)
3	**Severe**	• Clinically/medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; (CTCAE) • Health professional/clinical attention needed. Can be outpatient or inpatient. • Significant impairment in at least one domain of functioning[a], activities of daily living[b] or self-care[c] (>50% reduction in usual level)
4	**Very severe**	• Life-threatening consequences; urgent intervention indicated (CTCAE). • Includes suicidal ideation or attempt • If psychological in nature: requires in-patient hospitalization
5	**Death**	• Death
SERIOUSNESS (requires different reporting process)		
	Serious	• Grades 4 + 5 are serious; Grade 3 may be serious • Results in death • Is life-threatening • Requires hospitalization or prolongs existing stay • Results in congenital anomaly • Causes permanent disability or requires medical/surgical intervention to prevent permanent disability or any of the above.

[a] Domains of functioning = occupational (work), educational (school), social (friendships, community), role (parenting, spouse), cognitive (memory, decision-making).
[b] Activities of Daily Living (ADL) = preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[c] Self care = bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

OHRP. (2007). *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*: Office for Human Research Protections, US Department of Health and Human Services.
NCI. (2017). Common Terminology Criteria for Adverse Events (CTCAE) v5.0. *National Cancer Institute, NIH, U.S. Department of Health and Human Services*.
Linden, M. (2013). How to define, find and classify side effects in psychotherapy: from unwanted events to adverse treatment reactions. *Clin Psychol Psychother, 20*(4), 286-296.

Appendix C2

LIST OF PREVIOUSLY-REPORTED MEDITATION EFFECTS

(From Lindahl et al 2017 The Varieties of Contemplative Experience, *PLOS ONE*)

Affective Domain (13 Categories)	**Description**
Affective Flattening, Emotional Detachment, or Alexithymia	A narrowed or diminished affective range, a lack of affective charge, and/or an inability to identify/distinguish emotions.
Affective Lability	Rapid shifts in mood, mood swings, a increased range of emotions, or strong, unwarranted reactions to situations.
Agitation or Irritability	An agitated or irritable mood, possibly accompanied by restlessness, distractibility or uneasiness.
Change in Doubt, Faith, Trust, or Commitment	Changes (increase or decrease) in doubt, faith, trust or commitment in relation to religious doctrines, practices, goals, community or in relation to oneself in any dimension of life, such as self-confidence.
Crying or Laughing	Crying and laughing, and associated vocalizations.
Depression, Dysphoria, or Grief	Low, depressed, or sad moods, usually coupled with physical and behavioral manifestations that may or may not affect normal functioning.
Empathic or Affiliative Changes	Increased or decreased empathic connection to other people or to environmental stimuli.
Fear, Anxiety, Panic, or Paranoia	Feelings of fright or distress--with or without an external referent--and their corresponding physiological and behavior responses.
Positive Affect	A state of positive or elevated mood or energy level, ranging on a continuum from low to high arousal.
Rage, Anger, or Aggression	Feelings of intense displeasure or a retaliatory response, often caused by some adverse stimulus provoking an uncomfortable emotion.
Re-experiencing of Traumatic Memories or Affect Without Recollection	Either a recollection of some past traumatic event in the subject's life that may or may not have been repressed, and which is generally associated with strong emotions, or the upwelling of strong emotions without any corresponding memory, content, thought or other identifiable stimulus.
Self-Conscious Emotions	Emotions relating to one's sense of self and identity, as well as the awareness of reactions of others to oneself, whether real or imagined.
Suicidality	Affect-driven ideation concerning wanting to die, not wanting to continue with life, wishing to no longer being alive, thinking about taking one's own life, or thinking about or making specific plans for taking one's own life.

Cognitive Domain (10 Categories)	**Description**
Change in Executive Functioning	Either an inability to perform cognitive functions of decision making, concentration, and memory that the person used to be able to perform, or an enhanced ability in these domains of executive functioning.
Change in Worldview	A shift in ways of thinking about the nature of self or reality, including a change in understanding or confusion about the nature of self or reality.
Clarity	Reports of clarity or lucidity as a mental state, quality of attention, or quality of consciousness, in which there is a heightened cognition of relevant stimuli and a diminished interference from non-relevant stimuli.
Delusional, Irrational, or Paranormal Beliefs	Holding with conviction and being influenced by one or more beliefs despite evidence to the contrary. Ascriptions of significance or meaning that are later disregarded or that might seem unusual or concerning to members of the practitioner's broader culture or particular subculture. Attributions of paranormal agency, origin, or explanation for cognitive experiences.
Disintegration of Conceptual Meaning Structures	Percepts arise but are processed without their associated conceptual meaning, resulting in an inability to form conceptual representations of the perceptual world.
Increased Cognitive Processing	Primarily a cognitive change in thought amount or speed of cognitive processing, though the increase in processing often coincides with a decrease in sensory gating that leads to the impression of taking in or processing more perceptual information than usual.
Mental Stillness	An state in which there are few identifiable thoughts, a perceived absence of thought, or a poor awareness about the thinking process in general.
Meta-Cognition	Meta-cognition, or meta-awareness, refers to an explicit knowledge of the content of thoughts or the thinking process. Meta-cognition can also entail a higher-order cognition of processes in other domains of experience, such affective, perceptual, somatic or sense of self.
Scrupulosity	Obsessive thinking, specifically about moral or religious issues and behaviors.
Vivid Imagery	An experience of intense, vivid and/or clear thoughts or mental images that arise involuntarily, or a report of an increased ability to visualize.
Conative Domain (3 Categories)	**Description**
Anhedonia or Avolition	Anhedonia is the inability to experience pleasure in activities previously found pleasurable. Avolition is the lack of drive or motivation to pursue goals previously valued as meaningful.
Change in Effort or Striving	The degree or intensity of attempts at pursuing something valued-as-good or as a means to a valued end. Effort may be mental, physical, or emotional.
Change in Motivation or Goal	The reasons, drives, and needs behind a practitioner's actions, which influence or determine their behavior, as well as their expectations concerning a particular behavior.
Perceptual Domain (7 Categories)	**Description**

Derealization	Surroundings are perceived as strange, unreal, or dreamlike, or perception is experienced as mediated by a fog, a lens, or some other filter that results in feeling cut off from the world.
Dissolution of Objects or Phenomena	The dissolving or complete disappearance of visual objects or the entire visual field.
Distortions in Time or Space	An alteration in the subjective experience of spatial boundaries or relations and/or temporal causality or sequencing.
Hallucinations, Visions, or Illusions	A hallucination is an experience of a percept that is not externally stimulated, is not shared by others, and is not taken to be veridical. When a visual percept that is not shared by others is taken to be veridical, it is a vision. An illusion involves a percept that is distorted, changed, or has features added to the raw percept.
Perceptual Hypersensitivity	Unusual or atypical sensitivity to certain frequencies or volumes of sound (hyperacusis), to color (hyperchromia), to visual details, to light, to taste, to smell, or to embodiment.
Somatosensory Changes	A change in proprioceptive information that affects one's perception of relative positions or dimensions of body parts or the body more generally.
Visual Lights	Experience of a light or lights in field of vision that are vivid but not the result of external stimuli.
Sense of Self Domain (6 Categories)	**Description**
Change in Self-Other or Self-World Boundaries	Expansion beyond or distortions in the typical sense of where the boundaries between self and other or self and world are delineated.
Change in Narrative Self	A report of a change in how the practitioner conceives of himself or herself as a person. Or, a change in the content of or their perspective on their story or personal identity.
Change in Sense of Embodiment	Feeling of being disembodied, located outside or at a distance from one's body, or located in an unusual location within one's body schema.
Loss of Sense of Agency	A loss of a sense of ownership or sense of control over one's actions.
Loss of Sense of Ownership	A loss of the usual sense of owning one's thoughts, body sensations, emotions, and/or memories.
Loss of Sense of Basic Self	A loss of the sense of existing, of being a self, or of having a self.
Social Domain (5 Categories)	**Description**
Change in Relationship to Meditation Community	Changes in relationship with the meditation community (*Sangha*), whether increasing or decreasing degrees of affiliation with the community of teacher(s) and other practitioners.
Increased Sociality	Increased extraversion, social contact, friendships or other behavioral manifestations indicating an increased valuing of social engagement.
Integration Following Retreat or Intensive Practice	A destabilizing transition from intensive formal practice to informal practice, daily life, or life circumstances.
Occupational Impairment	An impaired ability to perform in an occupational environment.
Social Impairment	Behaviors indicative of a change in relationship to social networks or social situations that inhibits ordinary or desired functioning or level of engagement.

Somatic Domain (15 Categories)	**Description**
Appetitive or Weight Changes	Decreased or increased appetite, weight loss or gain.
Breathing Changes	Altered respiration rates that may manifest as a temporary cessation, or speeding up or slowing down of breathing.
Cardiac Changes	Irregular heartbeat, heart palpitations, or other significant irregularities.
Dizziness or Syncope	Dizziness, vertigo (feeling one is spinning or off-balance), lightheadedness (feeling one is about to faint), or syncope (a brief loss of consciousness and muscle strength, commonly called fainting, passing out or blacking out).
Fatigue or Weakness	A feeling of exhaustion, fatigue or weakness (general or localized).
Gastrointestinal Distress or Nausea	Gastrointestinal problems including (but not limited to) diarrhea, bloating, cramping, nausea and vomiting.
Headaches or Head Pressure	Ache, sharp pain, or pressure in the region of the head or neck.
Involuntary Movements	A motor movement usually under voluntary control that occurs without a conscious decision for movement.
Pain	Pain is an unpleasant physical sensation, either diffuse or acute, and lasting for variable amounts of time.
Parasomnias	Nightmares, vivid dreams, sleep paralysis or the alleviation of these symptoms.
Pressure, Tension or Release of Pressure, Tension	Bodily pressure or tension, or release of bodily pressure or tension, that can vary according to location (general or specific), intensity, or length of time.
Sexuality-Related Changes	Hypersexuality (very frequent or suddenly increased sexual urges or activity) or hyposexuality (notably decreased sexual urges or activity).
Sleep Changes	Changes in sleep amount, sleep need, or sleep depth.
Somatic Energy	A type of sensation moving throughout the body or throughout a body area described with language of vibration, energy, current, or other related metaphors.
Thermal Changes	Changes associated with heat or cold, whether a general change in sense of body temperature or localized to a specific body area.

Appendix D

Diabetes Doman Expected Events

Diabetes Domain (7 Categories)	**Description**
Cardiovascular	Angina, congestive heart failure, coronary angioplasty, coronary artery bypass surgery, coronary artery disease, dyslipidemia, hyperlipidemia, hypertension, myocardial infarction, stroke, transient ischemic attack (TIA)
Eye	Blindness, blurred vision, cataracts, detached retina, diabetic retinopathy, glaucoma, macular degeneration, macular edema, retinal laser photocoagulation, vitreous hemorrhage
Foot/Extremity	Amputation (not due to trauma), claudication, diabetic neuropathy, non-infected foot ulcer, peripheral artery disease, peripheral vascular disease, peripheral neuropathy (numbness, tingling or burning in hands or feet)
Glycemic	Hyperglycemia, hyperosmolar hyperglycemic state (hyperosmotic hyperglycemic nonketotic state), hypoglycemia
Infections	Cellulitis, coronavirus (e.g. COVID-19), Fournier's gangrene, infected foot ulcer, influenza virus (flu), pneumonia, pyelonephritis, sepsis, urinary tract infection, wet gangrene, wound infection, and other infections
Renal	Chronic kidney disease, diabetic nephropathy, proteinuria, renal disease, renal failure
Other	Fatty liver disease, obstructive sleep apnea, polydipsia, polyphagia, polyuria, weight gain, weight loss, and other expected events and symptoms in diabetes.