ClinicalTrials.gov ID: NCT03258723

Title: Diabetes Prevention with Lifestyle Intervention and Metformin Escalation (LIME)

Last Approved: 6/21/2021

Document: Protocol

HRP-503B – BIOMEDICAL RESEARCH PROTOCOL

Protocol Title: Diabetes Prevention with Lifestyle Intervention and Metformin Escalation (LIME).

Principal Investigator: Dr. Marcella Nunez-Smith

Version Date: version 7.0

(*If applicable*) Clinicaltrials.gov Registration #: NCT03258723

INSTRUCTIONS

This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:**

1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library.

2. If a section or question does not apply to your research study, type "Not Applicable" underneath.

3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

1. **Probable Duration of Project:** The expected duration of this project is 2 years
   State the expected duration of the project, including all follow-up and data analysis activities.

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2. Does this study have a Clinical Trials Agreement (CTA)?

Yes☐ **No☒**

a. If so, does it require compliance with ICH GCP (E6)?

Yes☐ **No☐**

3. Will this study have a billable service? **Yes ☐** **No☒**

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

4. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? **Yes ☐** **No ☒**

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? **Yes ☐** **No ☐**

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? **Yes ☐** **No ☐**

c. Will a novel approach using existing equipment be applied? **Yes ☐** **No ☐**

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**

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SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

   Specific Aim: Implement an evidence-based diabetes prevention pragmatic trial for high risk pre-diabetic individuals of Caribbean-descent to reduce the incidence of diabetes.
   Hypothesis: This study seeks to test the hypothesis that implementation of a lifestyle intervention, with escalation to Metformin therapy will lower the incidence of diabetes among the highest risk pre-diabetic individuals of Caribbean-descent.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

   Overview
   Despite over a decade of community based lifestyle only interventions, modeled on the Diabetes Prevention Program, the prevalence of diabetes among Blacks and Hispanic/Latinos has steadily and significantly increased.[1,2] Diabetes prevalence in non-Hispanic Blacks and Hispanics/Latinos is now 21.8% and 22.6% respectively, compared to 11.3% in non-Hispanic whites.[3,4] Given the limitations of lifestyle intervention alone,[5] current guidelines for the treatment of pre-diabetic patients include the option of pharmacotherapy with Metformin especially if there is a "history of gestational diabetes, age less than 60, BMI≥35kg/m2 and increasing hemoglobin A1c (HbA1c) despite lifestyle intervention."[6] The Diabetes Community Lifestyle Improvement Program (D-CLIP) in India was the first RCT to study the effect on pre-diabetic patients of step-wise escalation from lifestyle modification to Metformin prescribing, and showed a decreased incidence of diabetes.[7] Given the success of D-CLIP, the addition of pharmacotherapy shows promise in curtailing the frightening upward trend of diabetes prevalence among minorities.[8] A critical need exists for feasible and sustainable prevention interventions that use more than life-style intervention to reduce the incidence of diabetes.

   We will conduct a pragmatic trial that tests the effectiveness of lifestyle modification and Metformin use in minority populations. Our study population is Caribbean-descent individuals in Region 2, Barbados, Trinidad & Tobago. We will have six clinical intervention sites situated in New York – 2 (workshop feasibility and interviews only), Puerto Rico -1, the US Virgin Islands – 1, Barbados -1, and Trinidad & Tobago-1. These sites were chosen because of our strong research network in these locations, and to enable us to address diabetes disparities due to geographic differences.[9] We will first modify an established lifestyle modification workshop series developed by the East Harlem Partnership for Diabetes Prevention (EHPDP) for use in the community, [10]to target the population at the involved clinical sites. These workshops are based on an established Stanford Chronic Disease Self-Management Program that is validated and has been adapted to several different cultural settings. We plan to adapt the D-CLIP protocol and escalate to Metformin therapy for the highest risk pre-diabetic patients whose hemoglobin A1c (HbA1c) has not improved.

   We will leverage our existing robust research infrastructure and network at the six sites through our Eastern Caribbean Health Outcomes Research Network (ECHORN) and now the Yale Transdisciplinary Collaborative center for Health Disparities focused on Precision Medicine (Yale-TCC). ECHORN is a research collaboration funded by the NIMHD (U2458849938) to address the

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burden of chronic disease in USVI, PR and the Eastern Caribbean. The Yale-TCC (U54MD010711) leverages the infrastructure and knowledge of the ECHORN, expands to include New York and New Jersey and focuses on diabetes and hypertension (please note the Yale-TCC as a center works with New Jersey, but this study LIME does not have a site in New Jersey). Our network includes community advisory boards as well as policy delegations that are well suited to inform this project and its expansion into routine healthcare practice and policy.

Preliminary Studies

The flagship project of ECHORN has been the ECHORN Cohort Study (ECS), a unique cross-island collaboration including the US Virgin Islands (USVI), PR, Barbados, and Trinidad and Tobago. ECS was initiated in 2011 and designed to recruit and follow a community-dwelling adult cohort to estimate the prevalence of known and potential risk factors associated with the development of heart disease, cancer, and diabetes. To date, the ECS has empaneled almost 3000 adults who are ≥ 40 years of age, English or Spanish speaking, and who are residents on one of the islands. Preliminary analysis of ECS data has been important in confirming the burden of obesity and diabetes in the region and in framing our research questions and interventions. In ECS, preliminary results have shown that 72% are overweight or obese, 38% are obese (Class I, II and III). 25% of participants are pre-diabetic – classified by self-report or HbA1c of 5.7-6.4% or fasting glucose of 100-125 mg/dl. 25% were diabetic – again, classified by self-report, HbA1c≥ 6.5% or fasting glucose≥126 mg/dl.

Rationale

Our goal is to conduct a pragmatic trial that introduces a sustainable and feasible diabetes prevention intervention that combines lifestyle modification and Metformin prescribing to reduce the incidence of diabetes among the highest risk pre-diabetic patients. We utilize several rigorously done diabetes prevention studies to design a novel intervention that can be adopted in healthcare settings in a feasible and sustainable way. The first of these studies was the diabetes prevention program published in 2002.[1] Subsequently, there have been several adaptations of the DPP into community settings, one of which, supported by the NIMHD, was Project-HEED (Helping Educate to Eliminate Diabetes) developed by EHPDP.[10] HEED demonstrated the effectiveness of a community-based lifestyle intervention in achieving sustainable weight loss. D-CLIP was based out of an academic research center in India and demonstrated the effectiveness of stepwise escalation from lifestyle intervention to Metformin in reducing diabetes incidence.[7] Our proposed LIME intervention combines the evidence-based lifestyle intervention of HEED and Metformin escalation of D-CLIP into an effective and sustainable intervention in a healthcare setting (Table 1).

Table 1: Comparing LIME to other Diabetes Prevention Trials

Intervention Components	DPP	HEED	D-CLIP	LIME
Lifestyle Modification	X	X	X	X
Lifestyle + Metformin			X	X
US-based	X	X		X
Targeting Caribbean-descent individuals				X
Integrated into healthcare setting				X

The American Diabetes Association 2017 Guidelines recommend lifestyle modification as well as Metformin therapy for pre-diabetic patients.[6] The guidelines specify that “Metformin therapy for prevention of type 2 diabetes should be considered in those with pre-diabetes, especially for those

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with BMI ≥35 kg/m2, those aged < 60 years, women with prior gestational diabetes mellitus, and/or those with rising A1C despite lifestyle intervention." Despite this, there is little evidence of the effectiveness of lifestyle interventions in high risk pre-diabetics; the average HbA1c in DPP and D-CLIP was 5.9% and 6% respectively.[1,7] By focusing on the highest risk pre-diabetic patients with HbA1c of 6-6.4% we hope to add to the literature information on the effectiveness of lifestyle modification and Metformin in these individuals.

Our LIME intervention starts with lifestyle intervention and escalates to metformin therapy (prescribed by the participants primary care physician) to reduce diabetes incidence in high risk pre-diabetic individuals in Region 2 and the Eastern Caribbean. By starting with lifestyle intervention, our protocol is in line with the current ADA 2017 Guidelines that recommend Metformin therapy if HbA1c increases despite lifestyle. Additionally, guidelines recommend Metformin in all patients with a prior history of gestational diabetes and so this group is excluded from the study. The dose of Metformin to be used in diabetes prevention is not elucidated in the guidelines. DPP was done using a high dose of 850mg twice a day; a dose with known significant side effects. Limited data about the effectiveness of lower doses of Metformin for diabetes prevention among minority patients in the US is available.[8, 12] Therefore, we recommend that the participant's physician prescribing the Metformin start with a dose of 500mg of Metformin twice a day at 6 months. At the 12months follow up, patients whose A1c has continued to rise will get their dose gradually increased to 850mg twice a day or 1000mg twice a day based on availability.

The LIME study will be piloted in five sites across Region II and the Eastern Caribbean. This offers the opportunity to assess the replication of the study's culturally-tailored intervention framework for individuals of Caribbean descent, located in different geographic locations.

3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

Intervention Sites

The sites that will be implementing the LIME intervention are as follows:

a. *Internal Medicine Clinic at the University of Puerto Rico Hospital in Carolina* – Site PI: Dr. Elsie Cruz
b. *USVI Department of Health, Community Health Services* – Site PI: Lyna Fredericks
c. *University of the West Indies, Cavehill and Barbados Ministry of Health Polyclinics* – Site PIs: Dr. Joseph Herbert, Dr. Paul-Charles, Dr. Sobers-Grannum
d. *Southwest Regional Health Authority (SWRHA), La Romaine Health Center* (Trinidad&Tobago) – Site PI: Dr. Albert Persaud, Dr. Dale Sookoo

Sites that will be implementing only the workshops to assess for feasibility and acceptability of the workshops in NYC (participants here may be contacted for qualitative in-depth interviews after completion of the workshops):

e. *Union Community Health Center (Bronx, New York)* – Site PI: Dr. Vanessa Salcedo
f. *Internal Medicine Associates at Mt. Sinai (New York)* – Site PI: Dr. Victoria Mayer

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Sites that are only coordinating research activities and undergoing research analysis:
Emory University School of Medicine

Patient Recruitment:
We are targeting the highest risk pre-diabetic patients for this study. Patient recruitment will occur through the involved health clinics. The Research Assistant (RA) at each site will use either the Electronic Health Record (EHR) or paper chart to identify patients who meet the following eligibility criteria:

- ≥40-60 years old
- BMI≥23kg/m^2 or WC≥80/90cm
- No history of type I or type II diabetes or gestational diabetes
- Not on blood sugar altering medication
- Non-pregnant
- Linkage to healthcare provider to order medication and labs
- Health insurance to cover medication and labs
- Ability to attend weekly sessions
- Normal creatinine (If prior serum creatinine present in the record)

Individuals who meet eligibility criteria will be called in to participate in one of the study site's "Recruitment Days." Entry into a sweepstake for an I-Pad Mini will provide incentive for participation in the "Recruitment Day." All participants who attend the Recruitment Day (regardless of whether or not they enroll in the study) will be eligible to participate in the sweepstake.

We will also provide informational flyers to providers at each site (see attached flyers 1, 2 and 3) to encourage them to screen and refer patients to the study, In addition, we will post recruitment flyers in the waiting rooms of clinical sites aimed at garnering patient interest in the study. We will also have a patient tri-leaflet with pertinent study and study contact information.

Recruitment Day Procedure: here participants will hear more about the study and if interested will be formally consented (see consent process). Participants will then first undergo point of care (POC) HbA1c testing if they do not have an HbA1c result in their medical records from within 31 days of the Recruitment Date. If participants do have an HbA1c result from within 31 days in their medical records, that result will be used as their screening HbA1c value. If the measured or recorded HbA1c value is ≥6.5%, the participants will be excluded as they are possibly diabetic and will be referred to their primary provider for a confirmatory serum HbA1c test. If HbA1c<5.7, these participants are neither diabetic nor pre-diabetic and will be excluded. If HbA1c is between 5.7 and <6, individuals are pre-diabetic but low risk and are referred to their provider for routine care. Patients with HbA1c of 6-6.4% are deemed high risk pre-diabetics and can be enrolled in the study. Women of child-bearing age (age<50years) will undergo a urine pregnancy test to ensure eligibility for enrollment.

Control Participants
Control participants will be individuals who were identified as being eligible for the LIME study but who did not come to any of the workshops (deemed non-completers). These non-completers will be contacted 12-24months after their initial consent to ask if they would be interested in returning to the assessment center for follow up survey, clinical assessment, and laboratory studies. They will be provided an incentive for participation in the survey as outlined in the original consent form. Control participants will be reconsented (see new consent form) to outline that even though they did not participate in the intervention they can still obtain their follow up laboratories and compensation.

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New York Sites

The Union Community Health Center (UCHC) and the Internal Medicine Associates at Mt. Sinai (IMA) will not be recruiting patients for study purposes. At UCHC and IMA, providers will refer any patient with pre-diabetes who is interested to the LIME workshop. The patients with pre-diabetes will attend workshops and follow up with their provider as recommended. They will not participate in any survey, clinical assessment or laboratory studies.

A post-workshop evaluation that is standard as part of the curriculum is voluntary if participants would like to complete it at the end of the workshop series. This survey will only provide feedback on the workshop curriculum.

Participants and implementers (administration and workshop facilitators) will be asked if interested in participating in qualitative interviews. These individuals will be contacted and consented for in-depth interview participation (see qualitative interviews below).

Consent Process

Consent will be obtained by site RA trained in consenting participants. Consent forms will be available in English and Spanish (included with HIC protocol submission). Informed consent will be obtained at the prior to any data collection and participants will be asked to consent to being contacted for follow-up at regular intervals. Each subject will be assigned a unique ID that will follow them over the study period and beyond.

The following sites will have the option of obtaining the signed consent on REDCap: Barbados, Trinidad, and the USVI. These sites will have the option of obtaining signature of consent using the REDCap e-signature function on the REDCap data collection system. REDCap is a secure platform where no data is saved locally and all data is backed up automatically in a secure Yale server.

Sample Size:

The primary outcome of the LIME pilot study is reducing the hemoglobin A1c of high-risk individuals with pre-diabetes. The estimated total sample size of 250 participants (125 intervention and 125 control) is required to provide an 80% power to detect a ≥20% difference in proportion of individuals whose A1c drops below the high risk cut off of 6%-6.4%. Taking into account a ~ 20% loss to follow-up We need a total sample size of 330. Based on prior diabetes intervention studies,[1, 7] a statistically significant effect of the intervention on hemoglobin A1c will be seen at 12months. Control participants will be participants who were deemed eligible for the study but who did not attend a workshop (non-completers). These non-completers will be contacted 12-24months after their baseline assessment to guague their interest in returning for a follow up assessment.

Table 1: Sample distribution, assuming 10% attrition rate

	No. of Sites	**# Recruited *(10% attrition)***
Overall Sample Size		330
Barbados non-completers control Intervention	1	 40 40
Puerto Rico	1	

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Intervention		40
Trinidad & Tobago non-completers control Intervention	1	 75 65
USVI Intervention	1	20
New York – UCHC Control Intervention	1	00
New York -- Sinai Control Intervention	1	0 0

Baseline Assessment:
Consented participants will undergo a baseline clinical assessment (height, weight, waist circumference, hip circumference, waist-hip ratio, neck circumference, blood pressure), baseline laboratory testing and complete a survey.

Clinical assessment:
Basic clinical assessment will be done measuring height, weight, hip circumference, waist circumference, neck circumference, and resting blood pressure.

Laboratory testing:
HbA1c will already have been collected. For patients who do not have a cholesterol level or creatinine test in the medical record in the past 12 months, they will have blood drawn (15ml of blood) for cholesterol and creatinine. If creatinine is found to be elevated (contraindication to Metformin therapy), participants will be excluded and offered appropriate referral to a provider.

We will provide HbA1c point-of-care machines to all sites throughout the study; this is to ensure the consistency of the point-of-care testing. We will cover the costs of cholesterol and creatinine tests in Trinidad & Tobago as the Trinidad & Tobago Ministry of Health has a shortage of reagents, therefore limiting their capacity to test patients despite universal health coverage.

Survey:
A survey will be administered that covers basic socio-demographics, health history, physical activity level, food/beverage intake, social desirability scale and self-efficacy score.

All participants will receive written and verbal material about pre-diabetes and results of all their screening tests. They will undergo a basic clinical assessment for the following measurements: weight, waist circumference, neck circumference, hip-to-waist ratio, and resting blood pressure.

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Intervention

Figure 1: Intervention Schematic

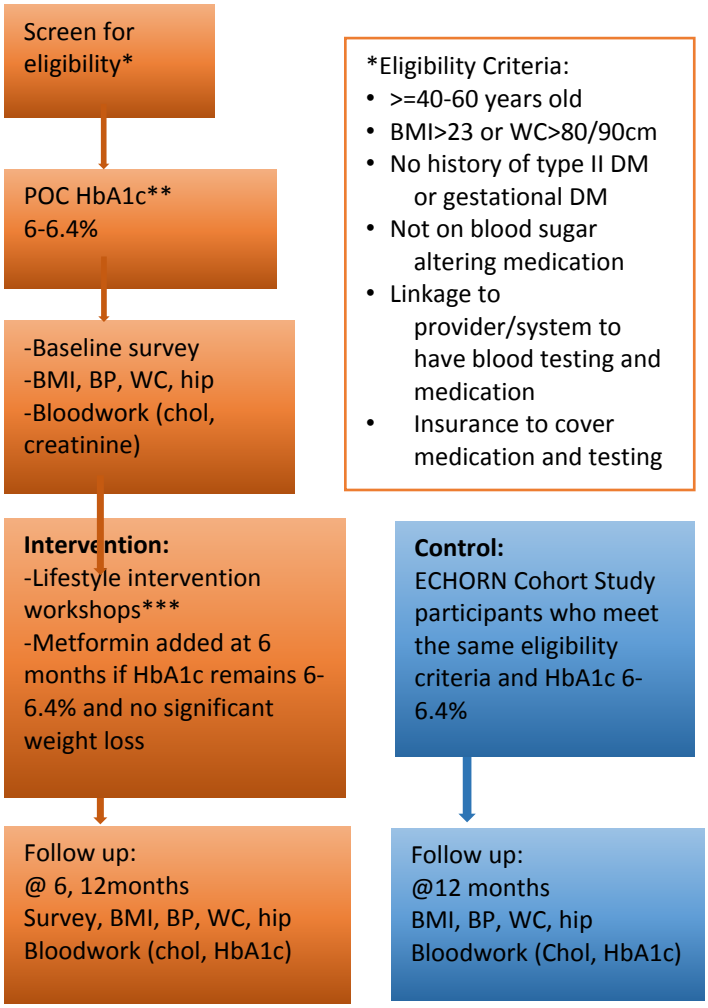

Figure 1 provides an overview of the LIME intervention

Lifestyle Intervention

The lifestyle intervention consists of a series of workshops adapted from the East Harlem Partnerships for Diabetes Prevention (EHPDP) that discuss diabetes prevention, finding and affording healthy foods, label reading, physical activity, planning a healthy plate, making traditional foods healthy and portion control. These workshops are based on the Stanford Chronic Disease Self-Management Curriculum.[13-16] It is a series of 6 weekly workshops each 2.5hours long. No incentive will be provided for attending the workshop as we are assessing feasibility of this intervention.

Staff will call participants to remind them of upcoming workshop sessions (see workshop follow up call script)

The newly launched EHPDP project's mobile app, iHEED will be used by intervention participants to help reinforce the content they learn during the workshop series. iHEED does NOT collect any Protected Health Information (PHI) and only offers lifestyle behavior modification resources and support. iHEED is designed to encourage group support and activities, provide updated news and information on diabetes prevention and tailor geographically- relevant resources to an app user's select needs (http:// projectheed.com/heed-app/).

Using mobile apps to influence healthy behavior such as healthy eating and increased physical activity links back to the theory of planned behavior, which posits that intended behavior (healthy eating and increased physical activity) is highly influenced by one's attitude towards the behavior, subjective norms and perception of behavioral control. [17] App usage has been associated with adoption and maintenance of healthy behaviors of healthy eating and physical activity. [18] Perceived effectiveness of health behavior-modifying apps has also been linked to the type of app user (multiple vs. single app user), duration of use, adherence measured via frequency of app use in an extended time frame, and goals setting. [18] Some participants will not have smartphones and not be able to use this app.

Post-workshop Survey:

At the end of the completion of the 6-week workshop series, participants will be given a short survey (GPAQ, NHANES DSQ, self-efficacy, choice of LSM sustainability approach). This additional survey will allow evaluation of sustainability of acquired healthy behaviors during the workshop series. This

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survey will be completed on paper and responses manually entered into REDCap by the RA or data coordinating center. The incentive for completion of this survey will be participation in a sweepstake for $400 prize.

Metformin Escalation
At 6 months, intervention participants who continue to have an HbA1c (determined by POC testing) to be between 6-6.4%, and have not had at least 5% weight loss, will have Metformin prescribed by their provider. Participants who have an HbA1c below 6% or have lost at least 5% of their weight will not have Metformin prescribed at 6 months. Metformin will be prescribed at 500mg twice a day.[12] There is data to support the effectiveness of lower doses of Metformin for diabetes prevention in Chinese and Indian populations, we do not have information specific to minority populations in the US.[12] Therefore, we will start at a low dose of 500mg twice a day. With the end of the subjects participation at the 12 month follow up visit, continued metformin doses (and whether to increase the dose or not) will be up to the provider's discretion and drug/dose availability. Written and verbal information regarding Metformin, common side effects will be provided to the participants. Participants will be given a nurse's number to call to discuss any side effects from the medication. Adherence to Metformin will be monitored by pill count – at scheduled visits with participant's primary providers or at LIME follow up visit at12-; a self-reported adherence measure will also be used.[19] It is expected that primary physicians who end up prescribing Metformin to the participants will routinely schedule their patients for a follow-up appointment in less than 6 months, to assess their performance on the new medication.

Metformin will be prescribed by the providers at the LIME clinic site. These are the primary care physicians who routinely care for the patients who are the LIME participants. These providers are not listed as co-investigators; this is an evidence-based intervention that is part of appropriate and routine care of their patients. These providers will attend 2 in-service sessions: 1. Study Protocol and parameters: this will be a description of the study rationale, protocol details, inclusion/exclusion criteria, monitoring and evaluation. 2. Metformin Prescribing: this second session will focus on the prescribing of Metformin for pre-diabetes and in the context of this study. Dosing of the prescription, how to educate the patient on side-effects of Metformin and when to contact the provider, and bringing the patient back in for follow up. Monitoring of whether Metformin is being prescribed per protocol will be done through intermittent chart review by the research assistant at each site.

The investigators do not have any existing clinical relationship with potential subjects. The investigators are affiliated with the institutions/clinics where the primary care providers deliver care to the LIME participants and will be prescribing Metformin. This affiliation allows them access to Clinic Provider Meetings and other information sessions. This will be the avenue through which, investigators and the research team, deliver information regarding the study and Metformin prescribing to the providers. At this time, there will be a discussion with providers around the evidence to support Metformin for this population and motivate provider adherence to the protocol and Metformin prescribing.

In Puerto Rico, the U.S. Virgin Islands, Barbados, and Trinidad patients' insurance will cover the cost of Metformin.

Follow-Up

Intervention Participants:
Follow up calls will be made with participants 3months after each visit to remind them of their engagement in the study and update any necessary contact information (See 3-month follow up call script).

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Intervention participants will be called back for follow up at 6, and 12, months. A $20 incentive will be offered at each follow up visit. At each follow up, the following will take place:

- *Clinical assessment:*

Repeat clinical assessment will be done measuring height, weight, hip circumference, waist circumference, resting blood pressure.

- *Laboratory testing:*

Laboratory testing at follow up will be done for HbA1c and Cholesterol (15ml of blood will be collected). HbA1c will be done by point-of-care (POC) machine every 6 months. If at any point of follow up the HbA1c becomes 6.5% or above; the patient will be informed that they may now be diabetic and need to get a serum test for HbA1c done by their provider. The result of the confirmatory serum HbA1c test must be subsequently reported to the LIME site to document incident cases of diabetes.

Cholesterol is covered by insurance not more frequently than every year, so will be checked at 12 months. As mentioned for baseline testing, we will cover the costs of cholesterol and creatinine tests in Trinidad & Tobago as the Trinidad & Tobago Ministry of Health has a shortage of reagents, thereby limiting their capacity to test patients despite universal health insurance.

- *Survey:*

A brief follow up survey will be administered that covers physical activity level, food/beverage intake, social desirability scale and self-efficacy score. At months 6 and 12 additional questions will be asked to assess the choice of sustainability approach that was used to sustain the LSM behaviors learned through the workshop series.

HbA1c changes at follow up

Patients will remain in the study for the duration of the study period regardless of whether their HbA1c increases or decreases. Figure 2 describes what happens at different time points in the study depending on changes in the HbA1c.

ECS Control Participants

Control participants will be individuals who were identified as being eligible for the LIME study but who did not come to any of the workshops (deemed non-completers). These non-completers will be contacted 12-24months after their initial consent to ask if they would be interested in returning to the assessment center for follow up survey, clinical assessment, and laboratory studies. They will be provided an incentive for participation in the survey as outlined in the original consent form. Control participants will be reconsented (see new consent form) to outline that even though they did not participate in the intervention they can still obtain their follow up laboratories and compensation.

At this follow up, they will undertake a survey, clinical assessment (weight, height, BP, WC, HC, neck circumference) and bloodwork (HbA1c and cholesterol) similar to the intervention participants. Of note here that the follow up interval for control and intervention participants is different. This is due to the fact that time from baseline differs depending on participant and island. A $20 incentive will be offered for each follow up visit.

New York Site Control Participants.

As New York's UCHC and IMA are not recruiting patients they will not need control participants.

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Figure 2: Decision tree for intervention participants based on HbA1c changes at follow up intervals of 6, and 12months

Primary and Secondary Outcomes

Our primary outcome for this pilot study is reduction in HbA1c. Prior studies including DPP and D-CLIP have shown a reduction in HbA1c in intervention arm within 6 months, so 12months should be sufficient to see a difference as well as any rebound increase in HbA1c. [7, 20] Our sample size has been powered to show a statistically significant difference in proportion of participants who have an HbA1c below 6-6.4% in the intervention and control study arms.

Secondary outcomes include: cholesterol level (cholesterol is a known risk factor for cardiovascular disease), weight, blood pressure, diabetes risk score, [21] self-efficacy score, [22] amount of physical activity (self-reported using the WHO Physical Activity Questionnaire, fruit and vegetable intake, sugar-sweetened beverage intake.

Data Collection

Data collection will occur at all baseline and follow up visits.

Prior to Recruitment

Prior to enrollment, staff at each clinic site will review the paper or electronic medical records of patients seen at each participating clinic. Clinic staff will keep a list of potentially eligible participants to be contacted for recruitment day. The clinic staff will contact the patient to inform them about the Recruitment Day and encourage them to attend so as to learn more about the LIME study and provide informed consent (see waiver of consent below). Staff will record the list of eligible participants, contact attempts, if they decline attending Recruitment Day, reason for declining, if accepting, date of Recruitment Day they will be attending, relevant clinic data (HbA1c, weight, height, creatinine and creatinine test date, last cholesterol level and cholesterol test date). This information is important in establishing reach of the intervention and also facilitate coordination on Recruitment Day. This form will be accessed through Vanderbilt University's Research Electronic Data Capture software (REDCap) and provides each patient a unique patient identifier.

Once recruitment is completed, we will de-identify all outreach REDCap data. This de-identified datea can then be used to evaluate characteristics of individuals who chose to participate in the study and those who did not.

At Baseline

The RA will complete an intake form with participants. This intake form will be administered through Vanderbilt University's Research Electronic Data Capture software (REDCap) and provides each

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participant a unique participant identifier. Participant's name and contact information will be included in the intake but this information will be stored separately from other patient-related data (de-identified). The REDCap instrument containing the participant names and contact information will be kept separate from the other REDCap instruments containing PHI. Access to identifying information will be limited to the site PI(s) and RA(s) at each LIME site. Additionally, each LIME site will only have access to their site's data, and a very limited number of individuals within each site will have access to the REDCap instrument containing PHI. All individuals with access to REDCap will receive extensive training in how to use the program and data confidentiality. The information in the LIME REDCap projects is temporarily stored on a tablets at each site when wi-fi/internet is not available. The information is backed up regularly to an online REDCap database and subsequently uploaded to a secure folder on a Yale Server.

Participants will have the option of completing the consent process in REDCap (they will still receive a paper copy).

Participants will complete the baseline survey on a computer using REDCap. The survey will be available in English and Spanish. A copy of the patient survey is included in the HIC protocol submission. The REDCap software also has a text-to-speech (TTS) functionality that enables the questions to be read out loud to participant filling out the survey. RAs will orient participants to the program and process and will be available throughout to provide assistance as needed. The questionnaire will take 35-40 minutes to complete and can be interviewer- administered in pen/paper format if preferred by the participant. Participants will take the survey on a tablet or desktop computer. Data from these participants will be stored only temporarily on encrypted tablet/computer if wi-fi/internet is not available. All survey data stored on the tablet and computers will be backed-up on a regular basis to the online REDCap database at the site and will be uploaded onto a secure folder on a server at Yale.

The clinical parameters will be collected in a private room; this will take 10 minutes. Weight will be obtained using an electronic scale. We will obtain blood pressure, hip to waist ratio, neck circumference, hip circumference and waist circumference readings twice and record the average of the results. These values will be entered into the REDCap database using a unique patient identifier.

Laboratory values include the POC HbA1c, cholesterol and creatinine. 15ml of blood will be collected from each participant to carry out these tests. These will also be recorded in REDCap as well.

At Follow Up
A brief follow up survey will be administered through REDCap as above. Clinical and laboratory parameters (POC HbA1c and Cholesterol only, 15ml of blood will be collected) will be collected and recorded in REDCap as at baseline.

Control Participants:

ECS participants are not able to be used as controls given COVID-19 restrictions limiting number of persons allowed in the assessment centers.

We propose contacting participants who screened in as eligible but never came in for a workshop or subsequent visit (non-completers), we would like to ask these participants if they would be interested in coming in to complete a a follow up survey and clinical laboratory assessment as outlined in the original consent form. We would offer this even if they did not participate in the intervention.

Additional COVID-19 Survey
An additional survey will be distributed to all participants who have attended at least one workshop to understand how the COVID-19 pandemic has impacted their ability to adhere to a healthy lifestyle.

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The LIME intervention relies heavily on the ability of participants to apply what they learned in the workshops regarding the maintenance of a healthy lifestyle. Unfortunately, the current COVID-19 pandemic has made it challenging to be active outdoors and obtain fresh fruits and vegetables. This survey is trying to capture participant ability to maintain a healthy lifestyle.
We will distribute the COVID-19 survey through the WhatsApp groups which most participants are members of. The participants will have a link. The link will take them to an informational page and consent addendum. We are requesting a waiver of consent for the COVID-19 Survey, so the participant will check the box in REDCap to provide non-signature documented consent. Once they consent they will be taken to the survey.

Table 2: Summary table of proposed data collection elements, frequency, and timing for LIME intervention study participants from baseline to 12 months

Schedule	Baseline	Year 1		LIME non-completers
Months	*0*	*6*	*12*	*12-24months*
POC HbA1c	•	•	•	•
Cholesterol	•		•	•
Creatinine	•			
Blood pressure	•	•	•	•
Weight	•	•	•	•
Height	•	•	•	•
Hip to waist ratio	•	•	•	•
Neck circumference	•	•	•	•
Baseline patient survey	•			•
Socio-demographics	•			
Past Medical History	•			
Family History	•			
Follow-up patient survey		•	•	•
Diabetes risk score	•	•	•	
Self-efficacy score	•	•	•	
Amount of physical activity	•	•	•	•
Dietary Screener Questionnaire	•	•	•	•
Medication Adherence	•	•	•	
Social desirability scale	•	•	•	
PROMIS Global Health	•	•	•	•
Choice of LSM sustainability approach		•	•	

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Quality control
Checks of data entry will be run by the data coordinating center at Yale every 2 weeks. This will entail ensuring that all participants have been consented (or re-consented as appropriate), all necessary data fields have been entered, incentive has been given as appropriate. For clinical assessment parameters, quality checks will include the assessment of clinically appropriate measures.

Data Analysis
Intention-to-treat analysis
We will adopt the intention-to-treat principle to analyze the data collected. We will compare participants' self-reported demographic characteristics at baseline, using bivariate comparisons with $\chi 2$ tests. We will also assess and compare changes in participants' HbA1c, BP, cholesterol, weight, waist circumference, fruit and vegetable intake, physical activity, diabetes risk prediction score, and self-efficacy score at baseline, 6 months, and 12 months, between the control and LIME intervention groups. We will perform two-sample t-tests and F-tests to show any significant differences between the study arms and repeated measures analysis to assess the longitudinal changes of study measures over the duration of the study. We will note here that the follow up intervals for intervention and control participants are different for practical reasons. This will need to be considered in the analysis.

Feedback
Feedback from participants and providers involved in the LIME intervention will be elicited through a text-based or email-based survey that will be sent out every 3 months..

Timeline

	Year 1			Year 2
Months of the Year	1-4	5-6	6-12	1-6
Intervention Months			1-6	7-12
IRB Approval by sites				
Staff training to conduct workshops				
Equipment purchase				
Staff train on POC machine				
Patient Recruitment and Enrollment				
Intervention				

Qualitative Interviews:
To understand the contextual factors that influence implementation effectiveness we hope to conduct in-depth interviews with participants and providers at each of our sites as outlined below.

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Interview Guide: the interview guide (see supplemental documents) is based on the Consolidated Framework for Implementation Research (CFIR) and seeks to understand, from the provider and participant perspective, the factors that influence the effectiveness of the intervention. The CFIR is an evidence-based, comprehensive, and practical taxonomy of constructs that influence implementation. The CFIR was developed by Damschroeder *et al* in 2009 to combine the many implementation theories that promote effective implementation but have different terminologies and definitions. It provides a list of constructs that have been shown to describe why, how, and where interventions work. Researchers can select constructs from CFIR that are most relevant to their study setting and use these to guide the design of interventions, evaluation of implementation progress, and post-implementation results.

Data Collection:
Research assistants (RA) at each of the 4 implementing study sites (Barbados, Trinidad, Puerto Rico, US Virgin Islands), already affiliated with ECHORN but not involved in the LIME study, will be trained on qualitative interviewing skills. This training will be a combination of online video tutorials on our established ECHORN training platform Schoology™, and online mock interviews with our team's qualitative experts. Using local RAs is critical to ensuring consistency in cultural and language fluency at each site. Four providers at each site will be interviewed and include an administrator, a workshop leader, a Metformin prescriber, and a front-line staff member. Four patients at each site will be purposively sampled to ensure at least two men and two patients on Metformin. The trained RA will conduct interviews at each site 6 months after the start of recruitment (June 2019-June2020). For quality assurance, we will convene a team of qualitative experts to review the first set of interview recordings from each site. A virtual meeting with all RAs will be held to provide collective feedback. A second similar session will be held after the third round of interviews. Interviews will be transcribed and translated to English when necessary.

On each island we will interview 4 implementers and 4 participants. These individuals are chosen randomly based on position/role in LIME (for implementers) and gender/workshop attendance (for participants).

Non-completer interviews
In addition, we will identify 2 participants who initially consented to being part of the study but subsequently decided not to attend the workshops. Since they did not come to the workshop these participants were considered non-completers of the study. These participants were contacted at least 3 times to schedule them into a workshop; only after 3 attempts are they then labeled as non-completers.

All noncompleters will be sent an email flyer asking them to complete a completely anonymous short survey via a link (survey in appendix documents). The flyer will also ask them to reply to the email with a phone number if they agree to be interviewed. Compensation of $25 will be offered if they are being interviewed. The interview will be conducted over the phone or on Zoom whichever is more convenient for the participant.

Consent process for noncompleters
For the interviews, the participant will be emailed a link to a consent form on REDCap. He/She can sign the online consent form. The interview will also repeat the consent over the phone to ensure no additional questions. [please note standard phone consent requirements cannot be followed as a result of the current COVID19 pandemic limiting ability to mail paper consent forms]

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NYC UCHC, Bronx Interviews
We will identify participants and implementers at the UCHC in the Bronx for in-depth interviews. We will use the same interview guide to address contextual factors that influence implementation effectiveness. The same qualitative interview consent guide will be used.

Analysis:
Coding will start immediately and will be iterative. Content analysis using the CFIR as a framework, will be used for coding. Future interview guides will be amended to further explore emerging themes that remain unclear or under-defined. More interviews may be needed to reach saturation. Team coding will be multi-disciplinary and include a Yale-TCC consortium/stakeholder member who has pre-diabetes but not involved in the study, a Caribbean-based research assistant, an expert in qualitative analysis, and Dr. Hassan. All team members will be trained on the use of the CFIR. We will also be open to new themes that arise inductively from the data. Applying previously described methodology, transcripts will be independently reviewed and team members will meet regularly to discuss emerging ideas, resolve discrepancies, and reach consensus regarding the codes. A case memo for each site will be generated organized by CFIR construct: where each construct has a summary statement with supporting quotes. Transcripts will continue to be coded, adding to the case memo. We will use ATLAS.ti™ (ATLAS.ti GmbH, Inc., Berlin, Germany) to facilitate data management and retrieval

Analysis of WhatsApp Data
During LIME Workshop sessions, each workshop group has spontaneously created their own WhatsApp group with all members of the workshop. Participants are free to post on the group, read postings, or remove themselves from the group as they see fit. On WhatsApp all members of the group have the ability to see who has read a message and who has posted a message. The research assistants **who are also the workshop leaders for that group** are all members of the WhatsApp group.

The purpose of analysing the WhatsApp data is to understand whether or not engagement in the group meant more engagement with the healthy lifestyle lessons that were learnt in the workshop. The hypothesis is that the more engaged someone was the more likely they were to adhere to lifestyle change. The second hypothesis is that a group that had engaged individuals was more likely to spill over to others in the group.

The WhatsApp group membership includes: all workshop participants and the 2 workshop leaders. We will be exporting the chat text from WhatsApp. WhatsApp has a chat text export function for this purpose. Anyone who has not consented for their data to be used will not have their information exported. Once exported we will de-identify all phone numbers/names and only use record ID numbers. The file with the chat and record ID numbers will be stored in a secure Yale Server. This will be a one time chat export at the 6months (2months window) and the 12months (2months window) follow up periods. At the 6-month mark, all data between the time the chat was initated and 6months is exported. At the 12months mark, all data between the 6months and 12months time point are exported. In between the chat export dates, there is no monitoring of participant activity so as not to contaminate the interaction.

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We will count the number of times each participant reads a WhatsApp message, and posts a WhatsApp message. We will then see if the number of posts/reads is associated with the sustaining healthy lifestyle change.

Please note that non-completer control participants do not engage in the WhatsApp Group.

Consent process for the WhatsApp Data:
We will send a link on each of the WhatsApp groups to a consent form (see WhatsApp consent). This will take the participant to a secure REDCap consent where they can approve or decline. Individuals who do not approve or decline will be called by the RA/workshop leaders to obtain consent over the phone. If consent is being obtained over the phone, the participant will still be asked to sign the REDCap consent form. [please note standard phone consent requirements cannot be followed as a result of the current COVID19 pandemic limiting ability to mail paper consent forms]
If a participant declines to have their WhatsApp data used. The WhatsApp group chat can still be used but any posts by that participant will be deleted and cannot be used for analysis.

4. Genetic Testing N/A ☒

A. Describe
   i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
   ii. the plan for the collection of material or the conditions under which material will be received
   iii. the types of information about the donor/individual contributors that will be entered into a database
   iv. the methods to uphold confidentiality

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
C. Is widespread sharing of materials planned?
D. When and under what conditions will materials be stripped of all identifiers?
E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
   i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

F. Describe the provisions for protection of participant privacy
G. Describe the methods for the security of storage and sharing of materials

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

Patients who are recruited into this study will be patients who seek care from these six clinical sites in Region II and the Eastern Caribbean:

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a. **Internal Medicine Clinic at the University of Puerto Rico Hospital in Carolina** – Site PI: Dr. Elsie Cruz
b. **USVI Department of Health, Community Health Services** -- Site PI: Lyna Fredericks
c. **University of the West Indies, Cavehill and Barbados Ministry of Health Polyclinics** – Site PIs: Dr. Joseph Herbert, Dr. Paul-Charles, Dr. Sobers-Grannum
d. **Southwest Regional Health Authority (SWRHA), La Romaine Health Center** (Trinidad&Tobago) – Site PI: Dr. Albert Persaud, Dr. Dale Sookoo
e. **Union Community Health Center (Bronx, New York)** – Site PI: Dr. Vanessa Salcedo
f. **Internal Medicine Associates at Mt. Sinai (New York)** – Site PI: Dr. Victoria Mayer

The patients will need to be English or Spanish speaking and meet the eligibility criteria outlined below. The socio-demographics of the patient population at these clinics are outlined below:

University of the West Indies, Cavehill and Barbados Ministry of Health Polyclinics
Practice location: Barbados
Patient demographics (race/ethnicity and gender):
--96% African Caribbean/Black
--70% Female

Southwest Regional Health Authority (SWRHA), La Romaine Health Center
Practice location: Trinidad and Tobago
Patient demographics (race/ethnicity and gender):
--42% African Caribbean/Black
--29% East Indian
--29% Mixed
--61% Female

Union Community Health Center, Bronx, New York
Practice location: New York (Bronx)
Large proportion Hispanic

Mount Sinai Internal Medicine Associates
Practice location: New York (Manhattan)
Patient demographics (race/ethnicity and gender):
--34% African American
--48% Hispanic (majority Puerto Rican)
--13% White
--5% Other
--66% Female

USVI Department of Health, Community Health Services
Race
--Black: 73.5%

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--White: 16.5%
--Other: 10%
Ethnicity
--Non-Hispanic: 97.1%
--Hispanic: 2.3%
--Not Reported: 0.6%
Gender
--Female: 65.8%
--Male 34.2%

University of Puerto Rico Hospital in Carolina Medicine Clinic
Practice location: Carolina, Puerto Rico
Demographics: all Puerto Ricans

6. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☒Non-English Speaking	☐ Prisoners	☒Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☒ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? **Yes ☐ No ☒**

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion Criteria:
- ≥40-60 years old
- BMI≥23kg/m^2 or WC≥80/90cm
- No history of type I or type II diabetes or gestational diabetes
- Not on blood sugar altering medication
- Linkage to a provider for medication prescribing and laboratory testing
- Health insurance to cover medication and laboratory testing
- Ability to attend weekly sessions
- HbA1c 6-6.4%

Exclusion Criteria:
- Pregnant
- Elevated creatinine with eGFR<45 mL/min/1.73 m^2

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8. How will **eligibility** be determined, and by whom?

Patient eligibility will be determined by the RA. The RA will use the EHR and paper health records at the clinical site to identify patients who meet the eligibility criteria noted above. Individuals who meet eligibility criteria will be called in to undergo point of care (POC) HbA1c testing. This will likely be done on a "Recruitment Days" for ease of scheduling. Participants will be consented and then have a POC HbA1c test. If the HbA1c value is ≥6.5%, the participants will be excluded as they are possibly diabetic and will be referred to their primary provider for a confirmatory serum HbA1c test. If HbA1c<5.7%, these participants are neither diabetic nor pre-diabetic and will be excluded. If HbA1c is between 5.7% and <6%, individuals are pre-diabetic but low risk and are referred to their provider for routine care. Patients with HbA1c of 6-6.4% are deemed high risk pre-diabetics and can be enrolled in the study. These participants will be eligible to enroll in the study.

Women of child-bearing age (<50years) will undergo a urine pregnancy test to verify that they are not pregnant prior to enrolling in the study.

Of note, for our NYC site, workshops will be offered to all individuals referred by their primary care physician for pre-diabetes; therefore, other study eligibility criteria do not apply as long as patient has pre-diabetes.

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

POC Testing and Venipuncture
Participants may experience a mild inconvenience during the POC HbA1c and creatinine when their fingers are pricked to have a drop of their blood drawn. Participants may also experience mild discomfort, pain or throbbing at the site of blood draw during venipuncture, when blood is drawn from their veins with a needle for the laboratory tests.

Time commitment
It may be time-consuming for participants to come to the clinic for testing at the beginning of the study and at 6 and 12 months. Attending educational sessions (6 total, each 2.5hours long) will also be time-consuming. Additionally, participants may not have adequate transportation, so travel to the sessions may pose an additional burden.

Privacy/Disclosure
Care will be taken to protect subject privacy, but the possibility of a data breach is always present. Participants in group education sessions will know the identities of other participants, thus the identities of the treatment group individuals with pre-diabetic glucose levels will not be confidential.

Metformin Medication
Risks associated with Metformin therapy are as follows:
-Mild possible side effects: diarrhea, gas, nausea
-Moderate (rare 1-10%) side effects: headache, dizziness, rash, decreased vitamin B12, weakness, chest discomfort, palpitations
-Severe (very rare <1%) side effects: lactic acidosis, megaloblastic anemia

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10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Participant compensation:
Participants will be compensated with a $20 gift card at each session; this should help minimize the inconvenience of coming in to complete survey, clinical assessment and laboratory testing. Additionally, participants in Puerto Rico will receive an additional $5 for parking fees or $10 for public transportation commute for study visits.

For in-depth interviews, participants will be given $20 for their time.

Workshop Benefits
Participants are expected to gain significant benefits from these educational sessions, both through joining a supportive community of other individuals working to control their weight, and through information sharing providing them tools for weight loss and lowering their risks for diabetes. It is expected that these benefits will outweigh the inconvenience of attending educational sessions. Standard protocol will be followed to minimize the risk of a data breach. It is expected that the social benefits participants will gain from participating in a supportive group that works toward the common goal of reducing diabetes incidence will outweigh the risk of losing anonymity through participation. Also, all participants will be told that participation in the trial is confidential and asked not to share the identities of other participants with others in their community.

Metformin therapy
To minimize risk of lactic acidosis, we will exclude patients who have renal insufficiency. Additionally, the Manual of Procedures (MOP) will explicitly note conditions for vitamin B12 level testing: history of anemia or peripheral neuropathy. This testing is indicated in the setting of Metformin therapy and should be covered by insurance. If not, it will be covered by the study.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study?

       We associate a greater than minimal risk level for participation in this study.

    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?

       Children will not be participating in this study.

    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://www.yale.edu/hrpp/forms-templates/biomedical.html for
        i. Minimal risk
        ii. Greater than minimal

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Greater Than Minimal Risk DSMP

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when re-approval of the protocol is sought). Any and all adverse events are to be documented in REDCap under the notes field in the clinical assessment for the appropriate time interval. Furthermore, it is immediately communicated to the study PI via email and/or phone. During the review process, the principal investigator (monitor) will review all note fields for documented adverse events, evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, or the IRB have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed greater than minimal for the following reasons:

1. We do not view the risks associated with Metformin therapy as minimal risks.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods; in particular Metformin drug therapy. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator Dr. Marcella Nunez-Smith according to the following categories:

a.) Definite: Adverse event is clearly related to the study.
b.) Probable: Adverse event is likely related to the study.
c.) Possible: Adverse event may be related to the study.
d.) Unlikely: Adverse event is likely not to be related to the study.
e.) Unrelated: Adverse event is clearly not related to the study.

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

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Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented**.**

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7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:

-All Co-Investigators listed on the protocol.
-National Institutes of Health

The principal investigator (Dr. Marcella Nunez-Smith) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

d. For multi-site studies for which the Yale PI serves as the lead investigator:
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?

A LIME Advisory Board (LAB) has been established that consists of regional stakeholders that are part of ECHORN/Yale-TCC, workshop leaders/trainers, and participants. This group meets at least twice a year, and quarterly if needed. The objective is to inform the LIME project and discuss and advise on any issues that arise. The PI, co-PIs and the RAs will be responsible for communicating adverse events and unanticipated problems to the data coordinating center at Yale via email reports with detailed description of these events and problems, as soon as they occur. These issues will be reviewed by the Yale coordinating center and the LAB as needed. Together a decision on the fit line of action to address the issues, and immediately report to the Yale IRB. All protocol amendments will be submitted as appropriate to reflect the actions/changes made to the study implementation, to tackle these events/problems. Anytime an issue is raised by the LAB, or a modification is made to the Yale IRB, local site PIs are informed. Subsequent to modification requests being approved at the Yale IRB, modifications are submitted to the local IRB in Barbados and Puerto Rico. The Yale coordinating center meets monthly with each of the site PIs to discuss any issues with the modification requests. Meetings are called more urgently if an issue is raised by the site teams or the LAB.

Monthly meetings with site teams have several purposes: quality assurance, quality review, review of any implementation challenges or issues, review of adverse events and plan of action, review of progress and timeline. Twice a year to quarterly, all LIME sites meet together with the LAB to discuss progress, challenges, and opportunities.

   ii. What provisions are in place for management of interim results?

The study seeks to collect baseline demographic, clinical, and self-reported measures. We will analyze results at baseline, and 6months of the study period. Each study participant will receive data on local healthcare providers for follow-up and any lab results will be sent to his/her healthcare provider upon request.

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iii. What will the multi-site process be for protocol modifications?

Site PIs do have flexibility in the language regarding demographic and some self-reported measurement data collection. The protocol for the collection of clinical data is set by the Yale-TCC at Yale and cannot be changed by site PIs. Regarding the protocols for which there is flexibility—allowing for language translation and cultural specificity (e.g., diet collection)—site PIs must present their proposed protocol to the Yale-TCC Implementation Core Alliance for review and approval.

Any protocol changes are first approved by the Yale IRB. Once approved, all changes and necessary documentation si communicated via email and follow up email to all sites. In Puerto Rico and Barbados, a local IRB modification request is then submitted for approval.

Quality assurance checks on the data are run every 2 weeks, these will incorporate checks on any protocol modifciations that have been made. Monthly LIME site meetings are an opportunity to discuss implementation of protocol changes.

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.

The primary outcome of the LIME pilot study is reducing the proportion of individuals with elevated HbA1c. Amon size calculation was estimated using a two-sample, paired t-test approach.

The estimated total sample size of 330 participants at each of the four sites (n=7150 total) is required to provide an 80% power to detect a ≥20% difference in proportion of individuals with HbA1c below the high risk range of 6-6.4%. This sample size takes into account a ≤ 10% loss to follow-up..

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒**N/A**

B. DRUGS/BIOLOGICS ☐**N/A**

Please note that Metformin will be prescribed by the physicians at the clinic site and dispensed at a local pharmacy. The Drug will not be stored or dispensed by the LIME team. The providers in the clinic who care for the patients are not members of the LIME study team. Follow up of the participant beyond the study period will therefore be undertaken by the primary provider for the patient who prescribed the Metformin initially. Subjects care in the clinic will be according to standard of care for that clinic

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

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Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☒
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☒
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☒
2. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☒
3. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☒

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

The drug Metformin and dosing at 500mg twice a day and 850mg twice a day is routinely prescribed, and FDA approved, for pre-diabetes. The risks associated with Metformin therapy are as follows:

- Mild possible side effects: diarrhea, gas, nausea
- Moderate (rare 1-10%) side effects: headache, dizziness, rash, decreased vitamin B12, weakness, chest discomfort, palpitations
- Severe (very rare <1%) side effects: lactic acidosis, megaloblastic anemia

3. **Source:** Identify the source of the drug or biologic to be used.

Participants will be prescribed Metformin by their provider in compliance with FDA regulations and ADA guidelines. The participants will obtain their Metformin prescription from a local pharmacy at their clinic site or area. These pharmacies are all appropriately certified. Pharmacies can obtain Metformin or generic form Glucophage.

a) Is the drug provided free of charge to subjects? ☐**YES** ☒**NO**
If yes, by whom?

Participants who are involved in LIME will have insurance that covers Metformin for pre-diabetes.

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After completion of the study, providers will be able to discuss with the participant continuation (or discontinuation of the Metformin). If continuing Metformin, providers can continue the dose of 500mg twice a day or they can increase the dose to 850mg twice a day or to 1000mg twice a day.

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

   Basic storage information for Metformin is as follows: keep container tightly closed. Keep container in a cool, well-ventilated area.
   Metformin is stable at room temperature
   Preparation/dispensing of medication as per pharmacy procedures

Check applicable Investigational Drug Service utilized:

☐ **YNHH IDS** ☐ **CMHC Pharmacy**

☐ **West Haven VA**

☐ **PET Center** ☐ **None**

☒ **Other:** Metformin will be obtained from the clinic pharmacy at each of the sites. Each of the sites outlined above have established and appropriately certified pharmacies that comply with all storage/preparation regulations for all medications including Metformin.

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation*.

5. Use of Placebo: ☒Not applicable to this research project

6. **Continuation of Drug Therapy After Study Closure ☐Not applicable to this project**
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☒ **Yes** If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.
Continuation versus termination of Metformin beyond the study period will be at the discretion of the physician caring for the patient. American Diabetes Association guidelines do not outline criteria for termination or continuation. As this drug is provided for by the participant's insurance, funding/access to the drug will not be an issue.

☐ NO If no, explain why this is acceptable. *Write here*

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. Targeted for enrollment at Yale for this protocol: 0.
b. If this is a multi-site study, give the total number of subjects targeted across all sites: 750.

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2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers	☐ Internet/Web Postings	☐ Radio
☐ Posters	☐ Mass E-mail Solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center Website	☐ Television
☒ Medical Record Review*	☐ Departmental/Center Research Boards	☐ Newspaper
☐ Departmental/Center Newsletters	☐ Web-Based Clinical Trial Registries	
☐ YCCI Recruitment database	☐ Clinicaltrials.gov Registry (do not send materials to HIC)	
☐ Other (describe):		

*** Requests for medical records should be made through JDAT as described at**
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

We are targeting the highest risk pre-diabetic patients for this study. Patient recruitment will occur through the involved health clinics. The Research Assistant (RA) at each site will use either the Electronic Health Record (EHR) or paper chart to identify patients who meet the following eligibility criteria:

- ≥40-60 years old
- BMI≥23kg/m^2 or WC≥80/90cm
- No history of type I or type II diabetes or gestational diabetes
- Not on blood sugar altering medication
- Non-pregnant
- Linkage to healthcare provider to order medication and labs
- Health insurance to cover medication and labs
- Ability to attend weekly sessions
- Normal creatinine (If prior serum creatinine present in the record)

Individuals who meet eligibility criteria will be called in to participate in one of the study site's "Recruitment Days." Entry into a sweepstake for an I-Pad Mini will provide incentive for participation in the "Recruitment Day." All participants who attend the Recruitment Day (regardless of whether or not they enroll in the study) will be eligible to participate in the study.

Recruitment Day Procedure: here participants will hear more about the study and if interested will be formally consented (see consent process). Participants will then first undergo point of care (POC) HbA1c testing. If the HbA1c value is ≥6.5%, the participants will be excluded as they are possibly diabetic and will be referred to their primary provider for a confirmatory serum HbA1c test. If HbA1c<5.7, these participants are neither diabetic nor pre-diabetic and will be excluded. If HbA1c is between 5.7 and <6, individuals are pre-diabetic but low risk and are referred to their provider for routine care. Patients with HbA1c of 6-6.4% are deemed high risk pre-diabetics and can be enrolled in the study. Women of child-bearing age (age<50years) will undergo a urine pregnancy test to ensure eligibility for enrollment.

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The following sites will have the option of obtaining the signed consent on REDCap: Barbados, Trinidad, and the USVI.

b. Describe how potential subjects are contacted.

Research Assistants will contact potential subjects through these avenues:

- RAs will reach potential subjects via phone calls to introduce the study to them and invite them to attend Recruitment Day
- RAs will coordinate with care providers to meet up with potential subjects to introduce them to the study during a scheduled routine clinic visit

c. Who is recruiting potential subjects?
Research Assistants (RAs) will recruit potential subjects.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:
Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?
☐ Yes, all subjects
☐ Yes, some of the subjects
☒ No

If yes, describe the nature of this relationship.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:
☐ For entire study
☒ For recruitment/screening purposes only
☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:

In order to identify participants who meet eligibility criteria, research assistants will need to access electronic health records to flag individuals who meet the eligibility criteria for the study noted above. These records contain the names and possibly, contact information of potential subjects that meet the study criteria. Without this information, we would not be able to contact potential subjects to tell them about the study. It is important to note that these clinical sites have existing and established treating relationships with these individuals, this forms the basis for the HIPAA waiver for this initial screening. Each clinical site will need to obtain additional IRB approval and HIPAA waiver approval through their affiliate institutions.

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ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data:

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

Informed consent will be obtained at the Recruitment Day appointment prior to any clinical or blood testing or enrollment of participants. Additionally, participants will be asked to consent to being contacted for follow-up at regular intervals. Each subject will be assigned a unique ID that will follow them over the study period and beyond. Consent will be obtained by the site-specific research assistant. This will be done in a space/office where participants can be consented in privacy. Separate consent form will be used to consent participants for qualitative interviews.

The following sites will have the option of obtaining the signed consent on REDCap: Barbados, Trinidad, and the USVI.

7. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

Clinical judgement will be used to determine participant ability and capacity to consent to the research being proposed. Given the age range of our participants – 40-60years of age – we do not anticipate any cases of dementia; therefore, mini-cognitive testing is not necessary. Clinical judgement will be used to determine participant ability and capacity to consent to the research being proposed. As all participants are patients within the clinic sites, research staff can consult with participant providers regarding participant ability and capacity to consent when needed. Any participant deemed unable to provide consent based on clinical judgement will have that determination confirmed by the participant's provider; that participant will then be ineligible to participate in the study.

8. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

All consent forms will be available in both English and Spanish. Consent will be obtained from participants by a Research Assistant fluent in the participant's native language. Those who are not fluent in English or Spanish would not be eligible to participate in the study.

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As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?
YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☒**Not Requesting any consent waivers**

☐**Requesting a waiver of signed consent:**

☐ **Recruitment/Screening only**

☐ **Entire Study (**Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? **YES ☐ NO ☐**
- Does a breach of confidentiality constitute the principal risk to subjects? **YES ☐ NO ☐**

OR

- Does the research pose greater than minimal risk? **YES ☐ NO☐**
- Does the research include any activities that would require signed consent in a non-research context? **YES ☐ NO ☐**

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☒ **Requesting a waiver of consent:**

☒ **Recruitment/Screening only**
☐ **Entire Study**

For a waiver of consent, please address the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***
  ☒ No
- Will the waiver adversely affect subjects' rights and welfare? **YES** ☐ **NO**☒
- Why would the research be impracticable to conduct without the waiver?
- Each clinical site will conduct chart reviews on their clinic patients to screen their patients for eligibility. Potentially eligible patients will be contacted by phone to inform them of the study and ask them if they are interested in attending a Recruitment Day event where they will get more information and sign an informed consent form. They will use a Recruitment Form, hosted on REDCap, to track outreach efforts and contact with participants. This REDCap database will be managed by Yale, which is an external coordinating site. The waiver of consent for recruitment/ screening only will allow the coordinating site to access and monitor the data obtained during screening and recruitment. The individuals conducting chart reviews and outreach to patients at these clinical sites have existing and established treating relationships with the patients.
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?
  No pertinent information is being collected to necessitate returning/sharing with subjects at a later date.

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Table 3. Proposed areas of LIME baseline and follow-up data collection

Self-Reported Measures	Clinical Assessment	Sociodemographic Characteristics
Fruit and vegetable intake	Weight/Height/BMI	Gender/Sex
Sugar-sweetened beverage intake	Blood pressure	Age
Physical activity	Waist & Hip Circumference	Marital/partner status
Self-efficacy score	Neck Circumference	Self-identified race/ethnicity
Medical history	Hemoglobin A1c	Occupation/occupational history
Family history	Cholesterol	Education
Medication adherence	Creatinine	Wealth
Social desirability scale		Insurance status

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In addition, the following HIPAA identifiers will also be collected from participants.

HIPAA identifiers:

☒ Names

☒All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

☒Telephone numbers

☒E-mail addresses

☐Social Security numbers

☒Medical record numbers for recruitment and screening purposes only

☒All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

b. How will the research data be collected, recorded and stored?

On Recruitment Days, all clinical assessment, point-of-care and survey data will be collected online into REDCap. The REDCap LIME project has a separate instrument that contains patient identifying information. All other instruments use de-identified participant ID. Sites will only be able to view data that is collected at their site. Select, trained, personnel will have access to the instrument containing patient identifying information, including contact information. Once data is entered into the REDCap system, it is immediately stored on a secure Yale server. In the event of no internet/wifi, data is temporarily stored on the provided tablets but then uploaded via internet to the Yale server. No data is locally stored on laptops, tablets or desktops.

In the event that a participant requests completing the survey on paper, that information will have to be manually input into the REDCap system. Only the participant ID will be on the survey, no identifying information. The paper survey will be scanned and securely emailed to the coordinating center. The paper copy will be destroyed.

All REDCap data is exported to SAS for later statistical analysis; files containing patient identifying information is kept separately. All files stored on a secure Yale server. Sites will not have access to PHI of other site participants.

Patients who consent for laboratory tests to be sent to their provider, will have those results sent to their provider once completed.

Quality assurance checks will be conducted every 2 weeks to ensure: consent has been obtained and documented, incentives as appropriate provided, accurate and complete data collection has been obtained. Quality assurance results will be communicated to site teams immediately, any issues addressed immediately when necessary and discussed further during monthly team meetings.

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c. How will the digital data be stored? ☐ CD ☒ DVD ☒ Flash Drive ☒ Portable Hard Drive ☒ Secured Server ☒ Laptop Computer ☒ Desktop Computer ☐ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

We are providing wi-fi access points to all sites that have unreliable internet. This will ensure that data collection can always be done online directly into REDCap. In select cases, de-identified data may be collected offline on tablets temporarily. This data will be uploaded, once wifi is restored, to a secure Yale server.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

There are no plans to destroy the identifiable data as the project may be interested in future extension and following participants into the future. However, the identifiable data links will all be stored at the TCC at Yale only on a single encrypted desktop computer that can only be accessed by the study PI and the Directors of the Yale-TCC.

f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

Only the study PIs, the Directors of the ECC and Yale-TCC, the project manager, and biostatistician will have direct access to PHI. Study site PIs may request PHI for participants at their site only and will be provided those data by the Directors of the ECC and Yale-TCC. Other research staff will not have access to PHI. De-identified data will be kept in separate, password protected databases from their code identifiers.

g. If appropriate, has a Certificate of Confidentiality been obtained?

N/A. A Certificate of Confidentiality is not needed.

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

There are no data collection points that require mandatory reporting.

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SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

Participants are expected to gain significant benefits from the lifestyle and educational sessions, both through joining a supportive community of other individuals working to control their pre-diabetes, and through information sharing providing them tools for weight loss and lowering their risks for diabetes. It is expected that these benefits will outweigh the inconvenience of attending educational sessions.

It is expected that the social benefits participants will gain from participating in a supportive group that all works toward the common goal of reducing diabetes incidence will outweigh the risk of losing anonymity through participation.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

   The alternative available to study subjects outside of the research is simply not participating in the study or going to their medical centers for screening.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

Participants will be given a $20 incentive at each follow-up. Participants in Puerto Rico will receive an additional $5 for parking fees or $10 for public transportation commute for study visits.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   The major cost to the participants is their time. Clinical assessments, including the laboratory tests for cholesterol would not be of additional cost to the participant. These costs will be covered by insurance. Metformin for prediabetes would also be covered by insurance. If for any reason, there are laboratory costs that are not covered by insurance, the LIME study will cover those costs.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   a. Will medical treatment be available if research-related injury occurs?

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b. Where and from whom may treatment be obtained?

c. Are there any limits to the treatment being provided?

d. Who will pay for this treatment?

e. How will the medical treatment be accessed by subjects?

4a-e: We do not foresee risk of physical injury as a result of taking part in this study. However, there is a small risk that a patient might be injured during the clinical assessment. Research personnel will be trained to dial 911 should any injury occur. A first aid kit will be in each assessment center which is managed by a licensed RN who can provide immediate first aid. Medical costs associated with any injury are the responsibility of the participant.

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