PROTOCOL

Randomized Explanatory Trial of a Mediterranean Dietary Pattern Weight Loss Intervention for Primary Care Practices

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Randomized Explanatory Trial of a Mediterranean Dietary Pattern Weight Loss Intervention for Primary Care Practices

(Brief Title: Med-South Weight Loss RCT)

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Sponsor: Center for Health Promotion and Disease Prevention (a CDC funded Prevention Research Center) at the University of North Carolina at Chapel Hill.

Grant Title: Randomized Explanatory Trial of a Mediterranean Dietary Pattern Weight Loss Intervention for Primary Care Practices

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CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

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STATEMENT OF COMPLIANCE

(1) [The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

For either option above, the following paragraph would be included:

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: Thomas C. Keyserling Date: 1/23/20/updated review 6/8/25

Name*: Thomas C. Keyserling, MD MPH

Title*: Professor of Medicine

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[For multi-site studies, the protocol should be signed by the clinical site investigator who is responsible for the day to day study implementation at his/her specific clinical site.]

Signed: Date:

Name:

Title:

Affiliation:

1 PROTOCOL SUMMARY

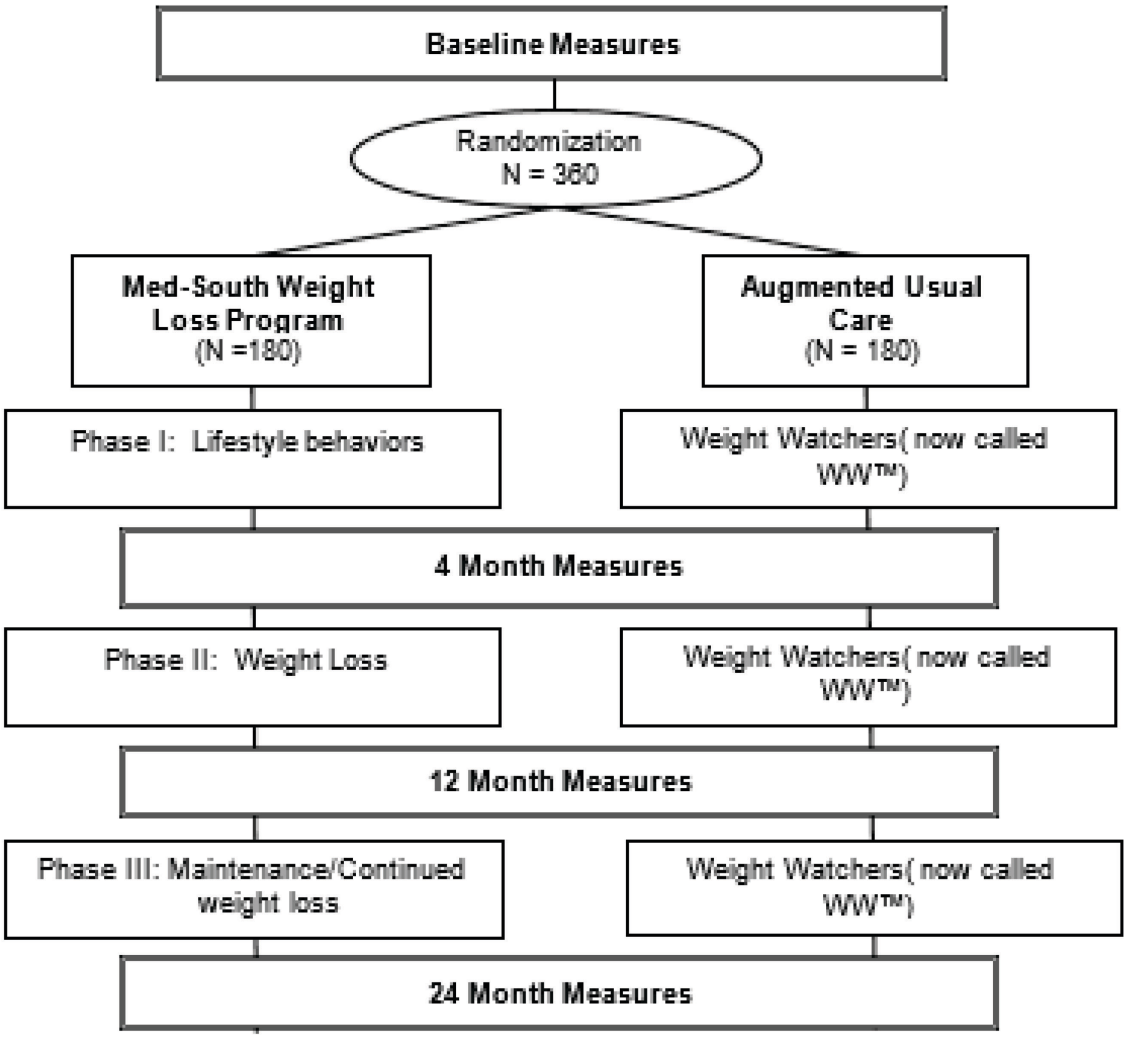
1.1 SYNOPSIS

Title:	Randomized Explanatory Trial of a Mediterranean Dietary Pattern Weight Loss Intervention for Primary Care Practices
Grant Number:	1R61HL142680-01A1
Study Description:	The US Preventive Services Task Force recommends primary care patients be screened for obesity and those with a body mass index (BMI) ≥30 kg/m^2 receive an intensive, multi-component behavioral weight loss intervention. However, the effectiveness of weight loss interventions implemented in primary care settings has been limited. Also, most weight loss programs have not promoted a dietary pattern associated with reduced rates for cardiovascular (CVD) and other chronic diseases such as a Mediterranean (Med)-style eating pattern. The DELISH (Delicious Eating for Life in Southern Homes) Study will test if a weight loss intervention emphasizing a healthful eating pattern (Med-style) can yield long-term weight loss and improved CVD risk profiles. Patients will be recruited from 5-8 primary care practices located in the Chapel Hill area and in eastern NC. Study participants will be randomized to the Med-Style Weight Loss Intervention or Augmented Usual Care (Weight Watchers™). The interventions are given free of charge. Study measurement visits are at baseline and 4, 12, and 24 month follow-up.

Objectives*:	**Primary Aim (efficacy):** Weight loss at 24 months. **Hypothesis:** Mean weight loss in the intervention group will exceed that in augmented usual care by ≥ 4% of initial body weight (e.g., ≥ 5% intervention, ~1% control). **Secondary weight outcomes:** Assess difference between study groups in proportion losing ≥ 5% body weight and differences in mean weight loss and proportion losing ≥ 5% across 3 pre-specified subgroups: 1) with vs. without diabetes; 2) females vs. males; and 3) Whites vs. African Americans. **Secondary Aim 1—Physiologic and Lifestyle Outcomes:** Assess change in blood pressure, A1c, markers of inflammation, skin carotenoids, and self-reported dietary patterns by study group. **Secondary Aim 2—Process and Psychosocial Factors**: Assess process variables (attendance, fidelity, and acceptability of the Med-style dietary intervention), and key behavioral and psychosocial variables, including self-regulation/monitoring skills, self-efficacy, motivation, and quality of life. **Secondary Aim 3--Economic Outcomes:** Assess implementation cost, and incremental cost-effectiveness of the intervention relative to control in terms of cost per percentage reduction in weight (i.e., kg lost) and cost per quality adjusted life years (QALYs) gained. **Exploratory Outcome—Stool Microbiome:** Assess change in stool microbiome in response to the interventions.
Endpoints*:	As outlined above under aims.
Study Population:	Participants will be enrolled in central and eastern North Carolina. The overall sample size is 360. We will conduct contemporaneous enrollment of sub-groups to ensure that at least 40% of participants will be African American, diagnosed with diabetes, and male.
Phase* or Stage:	Phase III
Description of Sites/Facilities Enrolling Participants:	Participants will be recruited from the UNC Department of Medicine Internal Medicine Clinic in Chapel Hill, at least 2 community practices within 20 miles of Chapel Hill, and at least 2 community practices from eastern North Carolina.
Description of Study Intervention/Experimental Manipulation:	The study intervention promotes a Mediterranean-style diet throughout the 2 year intervention period. (We use Mediterranean-style diet as a commonly recognized term for an evidence-informed dietary pattern--the intervention is Mediterranean Style, adapted for the southeastern US and informed by current evidence on dietary patterns and health outcomes). The Intervention has multiple contacts with study participants as outlined below. Format is individual counseling, face-to-face and phone, with the latter supported by web-based shared screen technology.
Study Duration*:	42 months
Participant Duration:	24 months

1.2 SCHEMA

Study Flow Diagram



1.3 SCHEDULE OF ACTIVITIES

The schedule of study activities is outlined in the flow diagram below. Please note, this diagram was prepared January, 2020 and is correct for Phase I study activities. As of January, 2020, Phases II and III are still being refined. These phases will be undated in Version 2 (for Phase II) and Version 3 (Phase III) of this protocol document. Also, please note the following study activities prior to Baseline Measures.

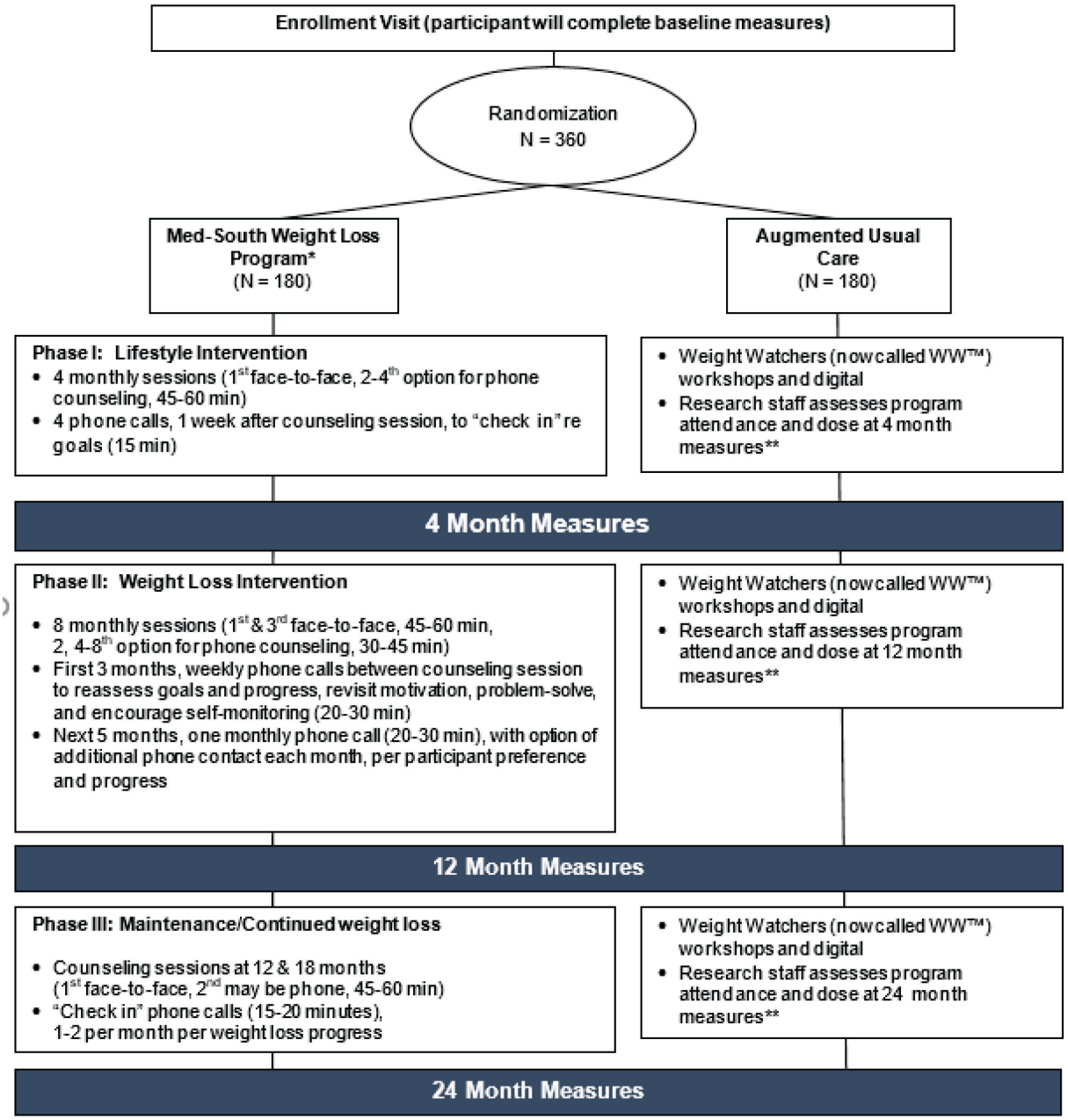
Recruitment and Enrollment will occur during two phone calls.

- Eligibility phone call. Patients who are referred to the study by their primary care provider will be called to assess interest and eligibility. Anticipated call duration is 10-15 minutes. If interested and eligible, the potential participant will be sent the study consent form and asked to review before the consent phone call.
- Consent phone call. This call is planned for 1-2 weeks after the eligibility call and is expected to last 20 to 30 minutes. Study staff will review the study in detail going over each key component of the consent form. If the potential participant agrees to participate, he/she will be invited to document consent through an IRB approved e-consent process. If the participant does not wish to use e-consent, he/she will give verbal consent and will sign the consent form at the enrollment visit, depicted on the diagram as "baseline measures." Note, the IRB has granted the study a waiver to collect baseline questionnaire data based on verbal consent. After the consent phone call, those who agree to participate will be encouraged to complete baseline questionnaires on-line (using REDCap) or by phone before the enrollment visit.

Allowable window for measurement and counseling visits.

- Allowable widows for measurement visits.
    - 4 month: 3-8 months.
    - 12 months: 11-18.
    - 24 months: 23-30.
- Allowable visits for counseling visits.
    - See flow diagram for sequence. The sequence will be followed as in the flow diagram. If a participant is falling behind the timeline, counseling visits may need to be truncated to allow the appropriate next measurement visit to occur within the allowable window.

Flow Diagram Outlining Intervention



*Counseling sessions: intervention format is web-based. Face-to-face counseling will be done using web-based interface. For phone counseling, participants have the option of accessing the web-based program or using a paper version.

**Data collection = number of program sessions attended, session format and duration. In addition, per data use agreement, WW will provide the following process measures: # of visits, use of digital program, weight at visits.

2 INTRODUCTION

2.1 STUDY RATIONALE

Note: the text for sections 2.1 and 2.2 is presented in Section 2.2

2.2 BACKGROUND

2.2a. *"Explain importance of the problem or critical barrier to progress that the proposed project addresses."*

Among adults with obesity, modest weight loss can prevent or delay the onset of diabetes, improved glycemic control in those with diabetes, and improve other physiologic risk factors for cardiovascular disease (CVD).[1, 2] Accordingly, the US Preventive Services Task Force (hereafter, called the "Task Force") recommends that primary care clinicians screen all adults for obesity and offer or refer those with a BMI ≥ 30 kg/m^2 to intensive behavioral weight loss interventions.[2] In formulating this recommendation, the Task Force "found adequate evidence that intensive, multicomponent behavioral interventions for obese adults can lead to an average weight loss of 4 to 7 kg (8.8 to 15.4 pounds).[2]

Despite the Task Force guideline endorsing intensive weight loss interventions, the effectiveness of weight loss interventions has been limited in both primary care and community settings. In a recent meta-analysis by Booth[3] assessing behavioral weight loss programs delivered in primary care settings, pooled results across 15 randomized controlled trials (RCTs) demonstrated only modest weight loss at 12 (-1.4 kg, 95% CI -2.1 to -0.6) and 24 month follow-up (-1.2 kg, 95% CI -2.3 to -0.2). Weight loss was also modest at 12 month follow-up (-2.2 kg, 95%CI -2.9 to -1.4) in a recent meta-analysis of 5 studies assessing commercial weight loss programs.[4] In his review on weight loss in primary care settings, Wadden[5] suggests primary care-based weight loss interventions often fail due to inadequate intensity for successful weight loss.

Weight loss is difficult to achieve and hard to sustain, especially for vulnerable patients (racial/ethnic minorities, rural patients, residents of the South) who are more likely to be obese, yet have been underrepresented in weight loss intervention studies.[6] Those with diabetes have an even harder time losing weight and maintaining weight loss.[7] This is especially true for African American women with type 2 diabetes.[6]

Emerging paradigms of care provide a framework for more effective clinic-based weight loss interventions. If an intervention is going to be implemented and sustained in routine primary care practice settings, its intensity should be aligned with practice staffing and it should be reimbursed. Wadden[5] suggests a team approach is needed to provide the requisite intensity (frequency and amount of contact time) for successful weight loss. He notes physicians typically do not have the time or training to give counseling, which might better be given by other staff (e.g., registered dietitians, medical assistants, nurses, etc.) -- the type of staff currently employed by patient centered medical homes (PCMHs).[8] Over 12,000 practices have PCMHs,[9] which have been shown to reduce the cost of care and[10, 11] improve care management for chronic diseases[11] including diabetes;[12] thus, they offer promise as a venue to deliver successful weight loss interventions.

Most weight loss interventions assessed in RCTs conducted in the US have NOT focused on promoting a healthful dietary pattern associated with reduced CVD events and total mortality. The Task Force "found inadequate direct evidence about the effectiveness of these (weight loss) interventions on long-term health outcomes (for example, death, CVD, and hospitalizations)."[2] Notably, most weight loss trials in the US have tested a low-fat dietary pattern,[1, 13-16] which is not associated with decreased CVD risk[17, 18] and is difficult to maintain over time.[17] With the publication of the PREDIMED RCT main results in 2013[19] (see information on retraction[20] and republication in June, 2018,[21] Sec. 1.2d), which demonstrated a 30% reduction in CVD events among those following a Mediterranean-style (Med-style) dietary pattern in Spain, there has been an increasing appreciation that a Med-style dietary pattern (or more generally, a healthful dietary pattern that includes generous consumption of high-quality fats[22, 23] and carbohydrates,[24-26]) is associated with improved health outcomes[27-29] including a reduction in CVD events and premature mortality.

Thus, the major problems that this proposal addresses are: 1) the limited efficacy of previously tested weight loss interventions conducted in primary care settings, 2) the lack of weight loss interventions that also promote a healthful dietary pattern, and 3) the scarcity of previously evaluated and effective weight loss interventions tailored to the needs of vulnerable patients.

2.2b**.** *"Describe the scientific premise for the proposed project, including consideration of the strengths and weaknesses of published research."* In this section, we address: 1) strengths and weaknesses of the Task Force recommendation for primary care clinicians to recommend weight loss interventions, 2) rationale for developing and testing a weight loss intervention promoting a Med-style dietary pattern, and 3) strengths and weaknesses of the literature on the efficacy of weight loss interventions promoting a Med-style dietary pattern.

Strengths and weaknesses of the Task Force guidelines recommending intensive weight loss interventions in primary care settings for patients who are obese. In the evidence review[1] for the Task Force, 21 behavioral weight loss studies with 12 to 18 month follow-up were included. The mean weight loss was 3.0 kg (95% CI, 2.0 to 4.0), but only 5 were conducted in primary care settings and only 2 of these in the US. Thus, more research on weight loss interventions given in US primary care practice settings is needed.

Rationale for developing and testing a weight loss intervention promoting a healthful dietary pattern. The Task Force weight loss recommendations apply to patients with and without diabetes. The prevalence of diabetes in the US is 9.4%, 25% in those over 65, and almost twice as common among African Americans.[30] As patients with diabetes are seen in clinic often, they account for ~40% of adult clinic visits in primary care.[31] In addition, about 1/3 of US adults have pre-diabetes (A1c 5.7-6.4%).[30] Because patients with diabetes and pre-diabetes are generally obese,[32] most patients seen in primary care who qualify for an intensive weight loss intervention per Task Force guidelines have diabetes or pre-diabetes. Adults with diabetes are about 2 times more likely to have a heart attack or stroke[33, 34] than the general population and those with pre-diabetes[35] and obesity without diabetes[36] are also at increased CVD risk. Thus, weight loss interventions should also target CVD risk reduction. Extending this further, weight loss interventions should strive to reduce premature mortality. These considerations represent a paradigm shift from the goal of weight loss to a goal of weight loss with a concomitant reduction in chronic diseases and premature mortality. This paradigm shift is supported by the emerging literature on dietary patterns and health outcomes,[19, 26, 28, 29, 37, 38] discussed in more detail below.

Why the Diabetes Prevention Program (DPP) dietary pattern may no longer be appropriate for a weight loss intervention. The DPP RCT[15] was a key proof-of-concept study providing strong evidence that a lifestyle intervention promoting weight loss can reduce diabetes incidence. Because of this important finding, the DPP lifestyle program has received a strong endorsement from federal,[39, 40] health professional,[41] and volunteer organizations[42] as an evidence-informed weight loss program for patients with or at risk for type 2 diabetes and is currently considered a standard of care. However, the dietary pattern advocated by this program[43] was developed in the 1990s[44] and one of its primary goals is a reduction in total fat. As noted in the next paragraph, there is now an emerging consensus that regular consumption of high-quality dietary fat is a key component of a healthful dietary pattern.[22, 23] Thus, the DPP weight loss intervention[45] advocating a low-fat diet runs counter to current scientific knowledge.[19, 22] Further, there is high-quality evidence from 2 large, well-conducted RCTs in those with and without diabetes that a low-fat dietary pattern does not reduce CVD risk. Look AHEAD, designed to see if a DPP-like weight loss intervention would reduce CVD events in overweight or obese patients with diabetes, was stopped early for futility[16] while the low-fat dietary intervention arm in the Women's Health Initiative RCT also failed to reduce CVD events.[17]

What type of dietary pattern should be advocated as part of a weight loss intervention? The PREDIMED RCT[19] compared a Med-style dietary pattern supplemented with olive oil or nuts to a control diet (lower fat diet) and observed a 30% reduction in major CVD events in the intervention arms, with a similar reduction in risk for the 49% (n=3614) participants with type 2 diabetes. Moreover, the intervention in this trial was associated with a 30% decrease in risk of developing diabetes,[46, 47] despite only minimal weight loss.[48] (In June, 2018, the PREDIMED primary outcomes paper[19] was retracted[20] due to recognized irregularities with randomization, and was republished.[21] After "omission of 1588 participants whose study-group assignments were known or suspected to have departed from the protocol," the findings were unchanged.) Though some will question the PREDIMED findings given the recognized irregularities,[49] it is important to note a prior secondary prevention RCT noted similar favorable results[50-52] and multiple well-conducted observational studies have associated healthful dietary patterns characterized by increased intake of high-quality fats[38] and high-quality carbohydrates[24-26] with reduced CVD risk, reduced premature mortality, and increased life-expectancy.[53] Indeed, a recent systematic review and meta-analysis of cohort studies[27] estimated that a healthful dietary pattern is "associated with a significant reduction in the risk of all-cause mortality, CVD, cancer, type 2 diabetes, and neurodegenerative disease by 22%, 22%, 16%, 18%, and 15%, respectively."

Healthful dietary patterns were highlighted in a recent publication[29] showing that those who changed to or followed more healthful patterns over time, as assessed by the Alternate Healthy Eating Index Score,[54] the Alternate Mediterranean Diet Score,[55] or the DASH score[56] had lower all-cause mortality. The dietary patterns rated highly by the Alternate Mediterranean Diet Score[55] and Alternate Healthy Eating Index[54, 57] are generally similar and do not focus on fat restriction, as does the DASH diet.[58, 59] Because the health benefits of a Med-style pattern are further supported by RCT evidence,[21, 50-52, 60] (the other patterns have not been studied to clinical outcomes in RCTs) we will advocate this general dietary pattern in our intervention, calling it Med-South, while recognizing this pattern could more generally be termed a healthful dietary pattern. As outlined in Sec. 3.3a, our operationalization of the Med-diet aligns extremely well with that described as evidence-based in a recent review by Mozaffarian[61] entitled, "Dietary and Policy Priorities for CVD, Diabetes and Obesity."

What type of dietary pattern should be advocated for maintenance of weight loss? There is an increasing appreciation that dietary composition impacts energy expenditure during weight loss maintenance and thus maintenance of weight loss.[62-65] In mechanistic weight loss studies, low glycemic

index and low carbohydrate patterns are associated with less reduction in resting energy expenditure.[62, 63] In support of this formulation are the long-term (6 year follow up) weight loss findings from the DIRECT RCT,[66, 67] with weight loss maintained in the Med-style and low-carb study arms (greatest in Med-style), but not in the low-fat arm. These data speak to the importance of attention to dietary composition in support of weight loss maintenance.

What are the strengths and weaknesses of the current literature on the efficacy of weight loss interventions promoting a Med-style dietary pattern? This topic was addressed in a recent systematic review (2016).[68] (Note, we conducted a PubMed search on 6/24/18 using the term "Mediterranean Diet Weight Loss" and did not identify other relevant RCTs conducted in the US, beyond those included in this review.) The authors reviewed 5 studies[66, 69-72] and concluded that the Mediterranean diet resulted in greater weight loss at ≥ 12 months than a low-fat diet and similar weight loss as other comparator diets (low-carb[66] and low-carb Mediterranean[69]). Three of these studies report weight loss at 24 months, with the Med-style interventions yielding ≥ 4 kg weight loss at this follow-up interval. However, the relevance of these 5 studies to obese patients in the US referred for weight loss by their primary care clinician is questionable. Two were conducted in Israel[66, 69] and one in Italy,[73] where the baseline dietary pattern is quite different from the US. The 2 US studies enrolled: 1) a sample from Boston, MA via letters to primary care physicians and posted flyers (82% white)[71] and 2) patients who had a myocardial infarction within the prior 6 weeks in Spokane, WA (98% white).[72] To our knowledge, no RCT has been conducted in the US on a primary care clinic enrolled multi-ethnic population that has tested a Med-style dietary pattern intervention for weight loss efficacy.

Thus, there is a strong scientific premise in support of conducting an RCT enrolling multi-ethic participants referred by primary care clinicians per Task Force guidelines to assess the efficacy of a weight loss intervention that promotes a Med-style dietary pattern adapted for Americans.

2.2c**.** *"Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields."* If successful, the findings from this study could have a significant impact on the challenge of managing obesity in primary care settings. Our findings will improve scientific knowledge and technical capacity to promote weight loss in a manner consistent with the emerging paradigm that weight loss studies should promote health behaviors associated with weight loss AND a decreased risk for CVD events and premature mortality.

2.3 RISK/BENEFIT ASSESSMENT

The potential risks of participating in this study are few. In the PREDIMED randomized trial,[20] there were no adverse reported outcomes related to the diet intervention. Similarly, in our recent Heart Healthy Lenoir study[74, 75] there were no reported adverse outcomes felt to be related to the dietary intervention. In this study, moderate physical activity will be recommended for both intervention groups. In terms of physical risk, it is unlikely that the recommended moderate intensity physical activity will provoke underlying medical conditions such as asthma, coronary heart disease, or musculoskeletal disease. Further, we will provide information on what to do if participants experience pain or other problems when being active. We will also provide explicit instructions to promote safety when walking for physical activity on streets or near highways. In addition, the risks of phlebotomy, though uncommon, include pain, fainting, local bruising, and infection at the puncture site. We do not foresee significant psychological, financial, legal or other risks from participation in this research study.

2.3.1 KNOWN POTENTIAL BENEFITS

Cardiovascular disease (CVD) is the most common cause of mortality for patients with obesity and diabetes and rates of CVD are high for obese patients with diabetes. There are high quality data suggesting that adhering to a Mediterranean style dietary pattern is associated with a substantial reduction in risk from heart disease and stroke. In addition, weight loss improves cardiometabolic risk factors and leads to other improved outcomes such as increased mobility, less joint pain, and less sleep apnea. Although participants in the study may not personally benefit over the relatively short time frame of the study, if they are able to maintain their lifestyle change, they may benefit over time.

Our hypothesis is that those who are randomized to the Med-South Weight Loss Program may benefit more than those randomized to WW, based on our expectation of greater sustained weight loss and greater improvement in traditional CVD risk factors such as blood pressure and blood lipids and emerging risk factors including markers of inflammation. That said, we anticipate those randomized to WW will experience some weight loss and improvement in risk factors.

2.3.2 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The potential risks are small, as noted above. We outline our approach to minimizing risk above. We believe there is much to be gained from this study, especially in the context of minimal risk.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
Primary Aim (efficacy): Weight loss at 24 months. **Hypothesis:** Mean weight loss in the intervention group will exceed that in augmented usual care by ≥ 4% of initial body weight (e.g., ≥ 5% intervention, ~1% control).	Weight change. (clarification: primary outcome is % weight change. Weight change in Kg will be a secondary outcome.	Primary outcome.	Weight loss is the anticipated outcome of the intervention.
Secondary			
Secondary weight outcomes: Assess difference between study groups in proportion losing ≥ 5% body weight and differences in mean weight loss and proportion losing ≥ 5% across 3 pre-	Weight change.	Weight loss of 5% or more is often an objective for weight loss studies.	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
specified subgroups: 1) with vs. without diabetes; 2) females vs. males; and 3) Whites vs. African Americans.			
Secondary Aim 1—Physiologic and Lifestyle Outcomes: Assess change in blood pressure, A1c, markers of inflammation, skin carotenoids, and self-reported dietary patterns by study group.	Change in blood pressure, A1c, markers of inflammation, skin carotenoids, and self-reported dietary patterns.	These are important, relevant physiologic and behavioral outcomes.	Weight change in response to a healthful diet will yield clinically important changes in these outcomes.
Secondary Aim 2—Process and Psychosocial Factors: Assess process variables (attendance, fidelity, and acceptability of the Med-style dietary intervention), and key behavioral and psychosocial variables, including self-regulation/monitoring skills, self-efficacy, motivation, and quality of life.	Process variables (attendance, fidelity, and acceptability of the Med-style dietary intervention) and key behavioral and psychosocial variables, including self-regulation/ monitoring skills, self-efficacy, motivation, and quality of life.	Process outcomes are important for understanding how well the intervention was given and psychosocial variables may provide insights on the intervention components associated with successful outcomes. These variables may be important moderators.	
Secondary Aim 3--Economic Outcomes: Assess implementation cost, and incremental cost-effectiveness of the intervention relative to control in terms of cost per percentage reduction in weight (i.e., kg lost) and cost per quality adjusted life years (QALYs) gained.	Implementation costs.	These data are needed for cost-effectiveness analysis.	
Tertiary/Exploratory			
Stool Microbiome: Assess change in stool microbiome	Change in microbiome	Emerging literature that microbiome composition is related to dietary intake.	Microbiome is associated with dietary intake.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
in response to the interventions.			

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label, randomized controlled trial enrolling 360 participants desiring weight loss and followed over 24 months. Participants will be randomized 1:1, stratified by practice and diabetes status, to either:

- Group 1: Med-South Weight Loss Program (the intervention);
- Group 2: Weight Watchers (WW™) (augmented usual care)

Randomized assignment will be done by a computer program stratifying on site and diabetes status and using randomly permuted blocks of random sizes for the randomization to achieve balance in the participants' allocation.

From the perspective of NIH, this is a single site study as the intervention is given by one investigational team. That said, participants will be enrolled from several practices in central and eastern North Carolina.

The acronym for the study is DELISH (Delicious Eating for Life in Southern Homes). The names of the study arms are given above.

WW™ was selected as the control group because we think it represents a current standard of care for a high intensity intervention that is generally available in both urban areas as well as smaller towns.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Rationale for study design and RCT overview: We propose an explanatory RCT to assess the efficacy of our weight loss intervention. As the type of intervention we propose has not been previously studied in a primary care setting (or otherwise) in the US, we believe there is sufficient scientific equipoise to undertake an explanatory trial. The primary focus of the intervention will be on dietary behaviors, though general information on physical activity will also be given (to the extent we anticipate this will be addressed in the augmented control group). Specifically, our focus is to isolate and study the effect of the proposed Med-style dietary pattern on weight loss. We propose a sample larger than needed to test

the primary outcome as it allows us to address secondary weight loss outcomes in 3 pre-specified subgroups: 1) those diagnosed with vs. without type 2 diabetes (hereafter, we will use "diabetes" to indicate "type 2 diabetes"), 2) female vs. male, and 3) whites vs. African Americans. All of these sub-groups will comprise at least 40% of the study sample. As we are proposing a behavioral intervention trial with the methodological challenges of a non-blinded RCT,[76] we will adhere to the updated (2017) recommendations outlined in the CONSORT statement for randomized trials of non-pharmacologic treatments.[76]

3.2c. Control group considerations: Current evidence suggests "usual care" dietary interventions in primary care settings are either absent (only 20% of patients with CVD, diabetes, or dyslipidemia receive clinic-based nutrition counseling),[77] ineffective,[5] or minimally effective (1.2 kg weight loss at 24 months).[3] However, given Task Force recommendations and ethical considerations for patients who enroll in a weight loss study, control participants will be offered a weight loss program of an intensity consistent with Task Force guidelines (WW™). It will be given free of charge, similar to the experience of the intervention group. Given prior success of weight loss interventions given in primary care settings[3, 5] and by commercial programs,[4] we anticipate weight loss at 24 months in our control group will not exceed 1.0% of initial body weight. As noted by Wadden,[5] weight loss in the control groups of studies conducted in primary care was typically < 0.5%, even among control participants who received augmented usual care.[78] As we recognize there will be some overlap in dietary pattern between intervention and control groups, we propose objective (skin carotenoids) and rigorous self-reported measures of dietary intake in both groups to assess the degree of overlap.

4.3 JUSTIFICATION FOR INTERVENTION

We propose individual counseling for the Med-South Weight Loss Group. Delivery by individual contacts (without group-based format as an option) is an adaptation based on: 1) contextual factors (e.g., poor patient uptake of group programs, time needed to train and supervise group facilitators, and logistical challenges) that could negatively impact group-based delivery in primary care settings,[79] and 2) advantages of individual contacts and evidence of comparable weight loss outcomes in group vs. individual treatment delivery.[3, 80] With this change, intervention delivery is made easier for staff in primary care settings, provides the advantage of a closer relationship between participant and interventionist, and allows tailoring of the intervention to fit the needs of individual participants. Participants who receive the WW™ intervention may attend group session (workshops) or use the WW™ digital interface for web and/or smart phones.

The number of contacts are similar to what we have used in prior weight loss studies[75, 81, 82] and consistent with the notion that successful weight loss programs require an intensive intervention.

4.4 END-OF-STUDY DEFINITION

The end of study is defined as completing the 24 month follow-up visit.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an identified patient must meet all of the following criteria.

Step 1—Identify patients from the electronic health record (EHR) who meet the following criteria

- age 18-75 (inclusive)
- BMI ≥ 30 kg/m^2
- do not have advanced kidney disease, defined as estimated glomerular filtration rate 30 mL/min/1.73 m^2 as assessed using the MDRD formula)
- have had a visit at the participating study site within the last 2 years.
- (effective 10/9/20): Weight less than 500 pounds. (For the rest of Wave 1 recruitment, we will ask potential participants about their weight and exclude if 500 pounds or greater. Starting with data warehouse pulls for Waves 2 and 3, participants will not be eligible if weight is 500 pounds or greater)

Step 2—Referred by the patient's primary care provider (PCP) to take part in this weight loss study. Operationally, the study provides a secure link to an Excel file listing the PCPs patient who qualify based on EHR review.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

Step 1--In thinking about making a referral to the study, we ask the PCP to consider each of the patient's clinical and social context. Please note, a patient **should not be referred** if any of the following apply:

- Does not speak English
- Too much medical comorbidity (such that a weight loss intervention is not a priority)
- Psychological or psychiatric reasons
- Has type 1 diabetes
- Prior bariatric surgery
- Malignancy other than non-melanoma skin cancer, unless considered cured > 5 years ago. Exceptions include 1) men with localized prostate cancer (treated with usual modalities or managed with "active surveillance"), and 2) postmenopausal women receiving adjuvant endocrine therapy (e.g., aromatase inhibitor) for non-metastatic, hormone receptor-positive breast cancer
- Alcohol or substance abuse
- Other reason (please include reason)

Step 2—During the eligibility telephone call, we further assess or re-assess the following.

- Interest: if not interested, excluded.
- Is anyone else in the household a participant? If yes, not eligible.
- Age: If less than 18 or over 75 at the time of the EHR review, not eligible.
- "Are you able to make changes to the food you eat? For example, we would not enroll someone who lives in a facility where a set menu is served?" If not able to make changes, not eligible.

- Are you able to access the internet by computer, tablet, or a smartphone on a weekly basis? If answer is no, not eligible.
    - (Above updated 11/24/20): Are you able to access the internet by computer, tablet, or smartphone on a weekly and, if so, are you comfortable using the internet for email and interacting with commercial websites. *(By "you," we mean the potential participant and not a family member. Examples of commercial web sites: banks, utilities, UNC MyChart, etc.)*
- Reassess prior bariatric surgery: If previous bariatric surgery, not eligible.
- "Do you plan to have bariatric surgery within the next year?" If answer is yes, not eligible.
- "During the past year, have you taken part in a formal weight loss program through your doctor's office or through a private organization like Weight Watchers™ (now WW™) where you have attended more than 12 sessions of the program?" If yes, not eligible.
- "Are you currently taking or in the prior 3 months have you taken prescription weight loss medication?" If yes, not eligible.
- "[For women, up to age 50] Are you pregnant, breastfeeding, or do you plan to become pregnant within the next year?" If yes, not eligible.
- "Have you had a problem with drug or alcohol misuse within the past 2 years?" If yes, not eligible. A problem is defined as alcohol use that interferes with work activities and/or has had a major negative impact on family/social function, the latter defined as more than 2 episodes per month.
- "Have you lost more than 20 pounds in the last 6 months?" If yes, not eligible.
- Recalculate BMI on self-reported height and weight. If < 27.5 kg/m^2, not eligible.
- Reassess type 1 diabetes. If yes, not eligible. (If participant not sure, we will check medical record and/or contact the primary care clinician.)
- Reassess cancer risk with algorithm that follows:
    - Have you been diagnosed with cancer other than skin cancer?
        - If yes, ask the following. (If no, not excluded.)
    - Have you been told you are cured of this cancer for 5 or more years?
        - If no, ask the following. (If yes, not excluded.)
    - Are you currently being treated for this cancer with medication or is surgery planned to treat this cancer?
        - If no, continue with the following. (If yes, not excluded.)
    - Let's assume it is OK for you to take part in this study so let's complete this survey but I will ask one of the study doctors to review your health record to see if you quality. It is possible he may want to speak with you by phone. We will be back in touch with you about this soon. After physician review, potential participant determined to be eligible.
        - If yes, potential participant is eligible. If no, participants is excluded.
- (effective 10/9/20): Participant unable to stand on scale unassisted. If yes, not eligible.

Additions to inclusion/exclusion criteria submitted to IRB on 11/16/20

- COVID-19
    - Mild disease: defined as asymptomatic, mildly symptomatic, or with moderate symptoms but not hospitalized. May start or resume study activities 30 days after diagnosis.
    - Severe disease with recovery: defined as requiring hospitalization, but recovered. May start or resume study activities 90 days after diagnosis or 60 days after hospital discharge, whichever comes first. Additionally, participant needs to convey they are

mostly recovered (90% or more back to normal). This will exclude the so called "long haulers."
    - Severe disease with persistent symptoms: defined as above, but without recovery at 3 month follow-up. Do not enroll and if enrolled, exclude for medical comorbidity.

- If a potential participant is referred by their primary care clinician of record on the date of data warehouse data review for eligibility, he/she may take part in the study if he/she changes primary care clinician, including a clinician outside the UNC system.

Refinement to eligibility protocol.

- After a potential participant completes the eligibility phone call, if deemed eligible, a study physician will review the patient's electronic health record to assess for any change in medical status since referral by the primary care clinician that would disqualify the potential participant and to confirm that the potential participant meets study inclusion criteria.
- Update 3/4/21—implementation information
    - Physician EHR review for eligibility started with Wave 1, Cycle 4.
    - Starting with Wave 1, Cycle 6 physician also reviewed for diabetes status, but eligibility protocol was not updated. Staff still askes potential participants about diabetes during eligibility interview.
- Update 3/4/21—protocol for EHR review
    - **Problem list** reviewed for 1) diabetes, 2) malignancy, 3) other diagnoses of concern including advanced cirrhosis, interstitial lung disease, etc.
    - **Medications** reviewed for diabetes, medications used for cancer, weight loss medication, and overall medical complexity of the patient.
    - "**Results Review** (lab tab)" reviewed re change in renal status since referral (eGFR < 30), diabetes, and for other medical conditions that might preclude participation.
    - **Cytology** reports for malignancy.
    - **Recent progress notes** by the PCP reviewed for overall health status of patient and any relevant diagnoses that might have been missed as above.

Addendum 11/4/21. Previously we have allowed HIV positive patients to participate who were considered stable and referred by PCP. This further defines stable. Stable now defined as RNA below the limit of detection and CD4 counts above 400.

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Follow the lifestyle recommendations for both dietary change and to be modestly physically active.
- If they are unable to make the recommended changes, they will continue in the study. Specifically, participants will not be excluded if they fail to achieve lifestyle goals.

5.4 SCREEN FAILURES

As noted in Sections 5.1 and 5.2, potential participants will be carefully screened for interest and eligibility before the enrollment. We anticipate the number of "screen failures" at the enrollment visit will be small and may occur under 2 circumstances.

- If a participant loses weight between the eligibility phone call (when BMI must be greater than 27.5 kg/m^2) such that the BMI at the visit is less than 27.5 kg/m^2, the participant is excluded.
- At our UNC internal medicine practice, 97% of patients identified have a creatinine in the EHR, which allows us to calculate estimated glomerular filtration rate (eGFR). Of these 3% have eGFR < 30 mL/min/1.73. We anticipate no more than 400 potential participants will attend the enrollment visit (goal enrollment is 360). Of these, we anticipate about 16 will not have creatinine to calculate eGFR. As a matter of participant safety (we would not want individuals with advanced renal disease to take part in the intervention), we will measure creatinine for these participants. Of these, we anticipate none will be excluded, but it is possible 1-2 could be excluded and this would be after randomization (randomization take places same day as blood draw).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Framework: We will recruit individuals within participating practices and will randomize 360 participants into one of two arms within practices. We will have 2 study locations: the Chapel Hill catchment area and a catchment area in eastern North Carolina. Participants enrolled in the Chapel Hill catchment area (Waves 1 and 2, see below) will have their measurement visits conducted at Center for Health Promotion and Disease Prevention, located at 1700 Martin Luther King, Jr. BLVD, Chapel Hill, NC. Those randomized to the Med-South Weight Loss Program will have their face-to-face counseling visits at this office. The location for study visits for the eastern North Carolina catchment area is to be determined.

To insure PCPs will be familiar with the majority of patients identified as eligible using the EHR, only PCPs who have been at the practice for 10 or more months will be invited to participate. We will enroll participants in 3 sequential waves, with a sample goal of 120 participants for each wave, as outlined below:

- Wave 1: Enrollment to start late March or early April, 2020. Due to a hold on research activities related to the Covid-19 pandemic, the first participant was enrolled 6/12/2020.
    - Participating site is UNC Chapel Hill Internal Medicine Practice (academic practice).
    - All PCPs (attendings and residents) who have been at the practice for 10 or more months will be invited to review their panel listings of patients who qualify and make referrals to the study.
- Wave 2: Community practices in the Chapel Hill area defined as within 25 miles of our research office at 1700 Martin Luther King, Jr. BLVD, Chapel Hill, NC. Enrollment to no later than October, 2020. Originally our plan was to enroll 2 practices. However, after first contacts with practices, we have learned that at some only a sub-set of clinicians might participate. Realizing some will decline, there is no minimum number of participating clinicians required for the practice to participate. Depending on the number of PCPs who participate and their panel sizes, we may

need to recruit from more than 2 practices. Ultimately, we identified a 3rd practice for Wave 2 enrollment.

- Wave 3: Eastern North Carolina. Enrollment to start no later than April 2021. We anticipate working with 2 practices, but it may be more than 2.

In January 2021, the investigators recognized 1) due to NIH budget cuts and 2) inefficiencies of setting up and staffing a second enrollment site, it would not be financially possible to set up a second enrollment site in eastern North Carolina. Thus, for Wave 3, instead of identifying and enrolling participants in eastern North Carolina, a decision was made to enroll at 3 additional practices located within 25 miles of our study office in Chapel Hill, NC.

Participants will be randomized within each site. Our primary rationale for randomization of patients and not practices is that weight loss interventions (both intervention and augmented usual care) are quite intensive and it is unlikely there will be significant contamination between intervention and augmented usual care participants (to minimize contamination only one member of a household may participate). Also, the intervention is given by research and not clinic staff (which also minimizes contamination). Randomization within practices allows for greater statistical power for the sample size enrolled.

Enrollment schedule:

				Participant Enrollment			
Grant Year-Calendar year	Calendar Month	Month of Enrollment		Wave 1	Wave 2	Wave 3	Total
1-2020	April	1		20			20
1-2020	May	2		20			40
2-2020	June	3		20			60
2-2020	July	4		20			80
2-2020	August	5		20			100
2-2020	September	6		20			120
2-2020	October	7			20		140
2-2020	November	8			20		160
2-2020	December	9			20		180
2-2021	Jan	10			20		200
2-2021	Feb	11			20		220
2-2021	March	12			20		240
2-2021	April	13				20	260
2-2021	May	14				20	280
3-2021	June	15				20	300
3-2021	July	16				20	320
3-2021	August	17				20	340

3-2021	September	18				20	360

Recruitment and retention of practices: Study staff will work with the North Carolina Network Consortium (NCNC) to identify and enroll study sites. All community study sites will be UNC Practice Network sites that use the UNC Health Care EHR. Retention of practices is not an issue because all we are asking practices to do is have their PCPs make referrals to the study and be willing to review routine study lab work (fasting lipid panel and A1c) as this is obtained at baseline and follow-up. Once a patient is referred, study staff will do all measures and will either give the intervention (Med-South Weight Loss Program) and refer to WW™ (augmented usual care).

Recruitment of individual participants:

Step-1--Identify potential participants from the Data Warehouse (DWH, also called electronic health record or EHR). The DWH is managed by the NC Translational and Clinical Sciences Institute (NC TracDS)

- Potential participants identified as meeting basic inclusion criteria by TraCS programmer using DWH (~2,900). Inclusion criteria are
    - Age 18-75 inclusive
    - BMI 30 or greater at last visit
    - Patient seen at practice during the past 2 years
    - Current PCP has been at practice 10 or more months.
- At UNC Internal Medicine Practice
    - Those who qualify are listed in Excel file (with identified data) made available to study staff. This will be stored in appropriate folder in Study's OneDrive account.
    - Study staff adds study ID # to the Excel file. This will be a 6 digit ID (and may increase to 7 digits if more than 9 sites). The first digit indicates site. The next is a separator 0 and then 4 digits listing potential participants at the site.
    - Study staff removes patients of study PI (Keyserling) and Co-I (S. Berkowitz)
- At Collaborative Center Coordinating Center (CSCC)
    - Programmer calculates eGFR and those with values less than 30 are removed from the dataset
    - Programmer selects a 50% random sample to create file of about ~1500 potential participants.
    - For community practices, will likely use entire listing.

Step-2—Study staff prepares Excel file for each primary care provider (PCPs)

Step-3—PCPs are sent email with information on how to complete the Excel file listing their patients who qualify for the study and a secure unique link to the Excel file (see letter below). An attachment or link to a one page document with more information about the study is also sent.

The PCP will be asked to refer patients to the study. In thinking about referrals, the PCP is asked to "consider each of your patient's clinical and social context. Please note, a patient **should not be referred** if any of the following apply:"

- Does not speak English
- Too much medical comorbidity (such that a weight loss intervention is not a priority)

    - Psychological or psychiatric reasons
    - Has type 1 diabetes
    - Prior bariatric surgery
    - Malignancy other than non-melanoma skin cancer, unless considered cured > 5 years ago. Exceptions include 1) men with localized prostate cancer (treated with usual modalities or managed with "active surveillance") and 2) postmenopausal women receiving adjuvant endocrine therapy (e.g., aromatase inhibitor) for non-metastatic, hormone receptor-positive breast cancer
    - Alcohol or substance abuse
    - Other reason (please include reason)
- At weekly intervals, we send reminder emails. A total of 2 reminders will be sent.
- At 2.5 weeks, Dr. Keyserling will try to reach those who have not responded by phone to encourage participation.

Letter to PCP

We are writing to request assistance in identifying your patients who might qualify for a weight loss research study, the DELISH (Delicious Eating for Life in Southern Homes) Study. Although the US Preventive Services Task Force "recommends that clinicians offer or refer adults with a body mass index (BMI) of 30 or higher to intensive, multicomponent behavioral interventions" for weight loss (Grade B recommendation), there is uncertainty about how best to achieve and maintain weight loss. Our research group at the UNC Center for Health Promotion and Disease Prevention has received funding from NIH to conduct a randomized trial comparing a new weight loss intervention promoting a healthful Mediterranean-style dietary pattern to Weight Watchers (now called WW™). Study participants will be randomly assigned to one of these programs (both given free of charge) for a 2-year period. (NOTE: The retail value of WW for 2 years is about $1000.) We think patients are likely to benefit from study participation and thus hope you will take the time to read the rest of this note and refer your patients to this study as appropriate. If you would like to learn more about the study, click here (add link).

With IRB approval (UNC IRB# 19-1712) and using the EHR, we have identified your patients who might qualify for this study: age 18-75 (inclusive), BMI ≥ 30, do not have advanced kidney disease, and have had a visit at the UNC Internal Medicine Clinic within the last 2 years. Below we provide a secure link to an Excel file listing a 50% random sample of these patients. (As we only plan to enroll 120 patients from the ACC practice, we are focusing enrollment efforts on a sub-sample of patients.) We ask you to consider referring these patients to the study. Patients randomized to the new weight loss program will a receive an intensive weight loss intervention that includes multiple counseling sessions with at least 4 sessions delivered in-person and the others in-person or by phone. Those randomized to WW will be encouraged to attended WW group sessions and/or use the WW digital intervention program.

In thinking about referrals, consider each of your patients' clinical and social context. Please note, a patient **should not be referred** if any of the following apply:

- Does not speak English
- Too much medical comorbidity (such that a weight loss intervention is not a priority)
- Psychological or psychiatric reasons
- Has type 1 diabetes
- Prior bariatric surgery

- Malignancy other than non-melanoma skin cancer, unless considered cured > 5 years ago. Exceptions include 1) men with localized prostate cancer (treated with usual modalities or managed with "active surveillance"), and 2) postmenopausal women receiving adjuvant endocrine therapy (e.g., aromatase inhibitor) for non-metastatic, hormone receptor-positive breast cancer
- Alcohol or substance abuse
- Other reason (please include reason)

Instructions for completing Excel file – As depicted in screenshot below from sample Excel file, for each patient:

- Type a 1 to indicate a yes response in the appropriate yellow, green, or pink cell.
- If you do not refer, please indicate why by typing 1 in the appropriate cell(s) to the right of the pink column. It is OK to indicate more than one reason.
- Study staff will call all referred patients to confirm eligibility.
- Study staff will conduct a chart review for patients you don't know well enough to consider for participation and will determine if patient should be invited to take part.

Don't know patient well enough to consider for participation	**Refer to study**	**Do not refer to study**	Does not speak English	Too much medical comorbidity	Psychological or psychiatric reasons	Has type 1 diabetes	Prior bariatric surgery	Malignancy, active treatment or not cured	Alcohol or substance abuse	Other	If other, specify reason
		1								1	Moved to DC
1											
	1										

Below is the link to the Excel file. Please note:

- After you click on the link, you will receive a passcode to access the file. If you do not receive it promptly, check your junk/spam mail.
- It is fine to scroll: the patients' names along with MRNs and column headings are "fixed" and will not move with scrolling.
- It takes about 5-10 minutes for every 20 patients listed.
- The Excel file saves all data automatically when entered. <u>You do not need to save this file</u>—just close when done.
- If not able to complete data entry, you can log back in using the same link at a later time/date.

[place link here]

If you have questions, please call or email Kiira Lyons, Project Manager, at 919-843-9563 or kiira_lyons@med.unc.edu.

Thank you,

Thomas C. Keyserling, MD, MPH

Professor of Medicine, Co-Principal Investigator

Carmen Samuel-Hodge, PhD, RD

Associate Research Professor of Nutrition, Co-Principal Investigator

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Step 4—Data from PCPs merged back into working Excel data file using the screening ID

- This file will now include a variable for those potential participants who are referred by their primary care providers to the study.
- If the PCP does not know the patient well enough to make a decision about a referral, the patient will not be invited to take part in the study. In other words, all study participants will be referred by their PCP to the study.

[Note, 2/26/20: Step 5 updated to allow enrollment goal of 40% for sub-groups with fewer potential participants available for enrollment.]

Step 5--Identifying potential participants to assess for eligibility with goal of contemporaneous inclusion of sub-groups (diabetes status, race and sex).

- We will undertake contemporaneous enrollment within each wave of enrollment for the study (Wave 1, UNC Internal Medicine Practice; Wave 2, community practices in Chapel Hill catchment area; and Wave 3, community practices in eastern NC).
-

Selecting participants to assess interest and confirm eligibility: Our goal is to enroll at least 40% of participants with diabetes, African American, and males and our plan is to enroll and achieve this ratio contemporaneously, through a series of cycles as outlined below. Our enrollment dataset will include participants' screening ID, diabetes status, sex, and race (from the EHR – we will ask participants to report race on our demographic form and this will be the official race variable). We anticipate that most of the potential participants will have been referred to the study by their PCP before we commence selecting participants for a Wave. However, if PCPs who are tardy in referring potential participants to the study do so after a cycle, their patients will be added to the pool for the next cycle.

We will invite participants to participate in sequential "cycles" separated by approximately 1 month. We anticipate about 1/4 of those invited will participate and our hope is to complete enrollment in four sequential cycles, so we will start with a cycle size of 120 for the UNC site (enrollment goal = 120) and 60 participants for each of the four community practices (enrollment goal per practice = 60). (If it turns out our recruitment strategy at community practices focuses more on clinicians than practices, as in 8 clinicians from 4 practices, we will adjust our numbers accordingly. We will consider this condition to

represent a virtual practice and will follow this protocol for contemporaneous enrollment of sub-groups as if it was one practice.) There are eight possible combinations from crossing the three sub-groups of interest (Table 1 below). In the first cycle at the UNC site, the list will include 120 potential participants with 12-18 potential participants per subgroup. To align with the pool of applicants, we will initially invite a minimum of 40% from each subgroups. We will select 1) 4 subgroups with the fewest participants in each cell or 2) (if subgroups are similar in size), the 4 subgroups with low Ns that includes those anticipated to be most difficult to recruit (e.g. males) for 40% enrollment. This approach should allow us to achieve a minimum of 40% in each subgroup.

Table 1. Number of potential participants per sub-group for the first cycle of screening

Subgroup	Participant with Diabetes	African American	Female	UNC		Other practices	
				N	%	N	%
1	Yes	Yes	Yes	18	0.15	9	0.15
2	Yes	Yes	No	12	0.10	6	0.10
3	Yes	No	Yes	18	0.15	9	0.15
4	Yes	No	No	12	0.10	6	0.10
5	No	Yes	Yes	18	0.15	9	0.15
6	No	Yes	No	12	0.10	6	0.10
7	No	No	Yes	18	0.15	9	0.15
8	No	No	No	12	0.10	6	0.10
			Total	120	100%	60	100%

When recruitment for a cycle is complete, the next cycle of eligible participants will be randomly selected from those unselected in the original screening list (i.e. from step 1) with weights for subgroups adjusted based on the observed yield of recruitment efforts in the prior cycle(s) using randomization procedures in SAS version 9.4. In other words, if males are under recruited, a greater number of males will be included in the next cycle for screening.

Updated 2/22/21

Modification for Enrollment for Wave 2

- Plan as discussed and updated at Investigator meeting 9/17/20
    - **Wave 2**:
        - In working w/ Jennifer Rees, (Practice-based Research Network practice facilitator), she had concerns that practices may not agree to participate (based on our early outreach before COVID) given all the stressors they are under and may be even more stressed with COVID.
        - So we pivoted to the option of inviting PCPs at practices to participate if they had been at the practice for more than 9 months. Our hope is that most will participate. We anticipate that we may need to work with **clinicians at 3-5 local practices to recruit/enroll 120 participants**. That said, the yield may be higher working with

local practices vs the geographically disperses patient population at the ACC practice.

As of 2/22/21: 3 local practices have agreed to participate

- Chapel Hill Internal Medicine (CHIM):
- Weaver Crossing (across the street from our research office)
- Orange Family Medicine

Modification to protocol for Wave 1:

- Recruitment cycles for community practice will include 60 potential participants instead of 120 as in Wave 1
- As of 2/22/21, Chapel Hill Internal Medicine has referred 329 potential participants with breakdown by subgroups as below. Of note, this practice is anticipated to have the lowest percentage of Black patients and patients with diabetes.
    - 11% Black: n= 36
    - 46% Male: n= 151
    - 15% Diabetes at least once: n= 50
- Given current high recruitment in Wave 1 of sub-groups of interest (55% African American and 45% with diabetes), we will set targets as follows for this practice:
    - Blacks: 30%
    - Diabetes: 35%
    - Male 40%

Note on contemporaneous enrollment entered 6/8/25.

V. Contemporaneous enrollment outcomes

For Wave 1, given the size of the academic practice and our expectation that ½ of the sample might yield 120 participants, we initiated enrollment by drawing a 50% probability sample (n = 1435) and preparing a referral spreadsheet for each PCC from this subsample. We followed our protocol for contemporaneous enrollment of subgroups, as described above, and after Cycle 3 (approximately 360 participants invited to participate), we had completely depleted patients in 2 subgroups of interests (African American females and males with diabetes). To allow for continued enrollment of all sub-groups of interest, we initiated a second round of enrollment during Wave 1 from the remaining sample (n = 1434), excluding 239 patients whose PCC's were 3rd year residents who had graduated from the program. From this second round of referrals, we prioritized invitations to those in our subgroups of interests.

For Wave 2, which included 2 internal medicine and 1 family medicine practice, the number of patients identified from the Data Warehouse ranged from 418 to 534 per practice, with a smaller percentage of patients who were African American or patients with diabetes. For these sites, we invited all African American and patients with diabetes to participate, as well as most of the white men.

For Wave 3, which included 2 family medicine practices and 1 internal medicine/pediatrics, the number of patients identified from the EHR ranged from 234 to 351. During Wave 3, the study met is quota for white females without diabetes. Accordingly, the names of 151 white females with diabetes were not included on referral spreadsheets distributed to Wave 3 PCCs; all identified as African American, patients with diabetes, and male were included on these spreadsheets.

Step 6—Contacting participants identified in Step 5 to assess eligibility and interest

Mail information brochure and cover letter to potential participants identified as outlined above and request that within one week, those who 1) know they are interested or 2) know that they are NOT interested send us an email or call to provide this information. Place those who express interest on our call list.

- Approximately 10 days after mailing, start calling those who we do not hear from. Our call protocol is as follows:
    - We will call up to 5 times over a 2 week period. We will attempt 2 calls during regular work hours (8:30 to 5:30 on weekdays) and 3 after hours, including Mon-Thurs evening between 5:31 and 9:00 pm and on Saturday calling between 8:30am and 5:30 pm.
    - We will leave up to 2 phone messages.
- During eligibly calls, data are entered into the REDCap eligibility questionnaire. This form also has fields for tracking information on attempted calls for the phone call.
- If a potential participant is interested and eligible, staff will either mail or email the consent forms to this individual and an appointment will be made for the consent phone call in about 1 week.

Step 7—Study staff updates the Excel data base based on eligibility phone call.

- Status variable
    - 1 indicates potential participant agrees to be contacted again for Consent Phone call.
    - 2 indicates potential participant contacted, but not interested. Identifying data is removed. (Name, DOB, address, and phone #).
    - 3 indicates potential participant contacted and is interested, but not eligible. Identifying data is removed. (Name, DOB, address, and phone #).
    - 4 indicates potential participant never contacted by phone. Identifying data is removed. (Name, DOB, address, and phone #).

Step 8—Consent phone call

- At this phone call, key components of the consent form are reviewed in detail to insure that the potential participant understands what participation entails. During the phone call, the "Stored Specimens with Identifiers" and "HIPAA Authorization" are also reviewed. It the potential participant agrees to sign consent form via e-consent, instructions are given on how to do so. If the potential participant prefers to sign at the enrollment visit, then verbal consent to complete baseline questionnaires before the enrollment visit will be obtained, as approved by the IRB.
- Instructions for completing baseline forms, on-line or by phone, are given and plans to complete these forms are made accordingly. An appointment date is set for the baseline visit.
- Parameters for contacting the patient are the same as for the eligibility phone call outlined in Step 6.

Enrollment visit and randomization: At the enrollment visit, all questions will be answered about the study and those who did not sign the consent forms on-line (e-consent) will sign the consent form. Upon completion of baseline measures (except for the stool sample) the participant will be ready for randomization. The research assistant will use the randomization function in REDCap to ascertain randomization assignment.

Insuring enrollment of "vulnerable populations": We will purposefully recruit vulnerable populations (low-income and minority patients) primarily through our selection of study sites that serve a large population of vulnerable patients and also recognizing that these populations are overly represented among those with obesity and diabetes.

Retention of individual participants: To enhance retention of participants, at enrollment, we will ask for home and cell numbers, if it is OK to send text messages, and if it is OK to contact by email and/or the web communication function of the EHR (at UNC, this is called MyChart). We will also ask participants to provide contact information for an alternate contact (friend or family member) in case we are unable to reach them directly. In attempting to schedule a follow-up contact, we will allow up to 5 attempts to reach a participant over a 2-week period and up to 3 attempts to reach the alternative contact. Our goal is to contact participants who are late for study activities early and often in support of their participation. Though we will promote participation in a timely fashion as much as possible, we will also respect study participant's desire to withdraw from the study at any time.

Incentive for participation: Their weight loss interventions (both Med-South Weight Loss Program and WW™) are given for free. Measurement visit at baseline and 4, 12, and 24 months are compensated at the rate of $60, about $20-30 per hour. Travel for measurement visit greater than 20 miles is compensated at the state of NC compensation rate. We do not think this compensation is coercive and think the rate is in line with what the IRB typically endorses for measurement visits. To enhance follow-up at 24 months, compensation was increased to $100.

Possible competition from other trials, secular trends, and co-interventions: We do not anticipate major competition from other weight loss trials. However, if others are funded, as outlined above, we believe there are ample numbers of patients with obesity for our trial and others. It is unlikely that secular trends will have a major impact on weight change, but if they do, they should have similar impacts across our two study arms. Similarly, co-interventions such as diabetes medications that are associated with weight loss would likely be equally distributed across study arms. If not, we could control for this factor in the analysis as we are assessing specific types of medications for diabetes. Finally, participating sites may begin to routinely offer more effective weight loss programs. However, all our participants should be taking part in our study weight loss interventions, so it is unlikely that such programs would have a major impact on study participants.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

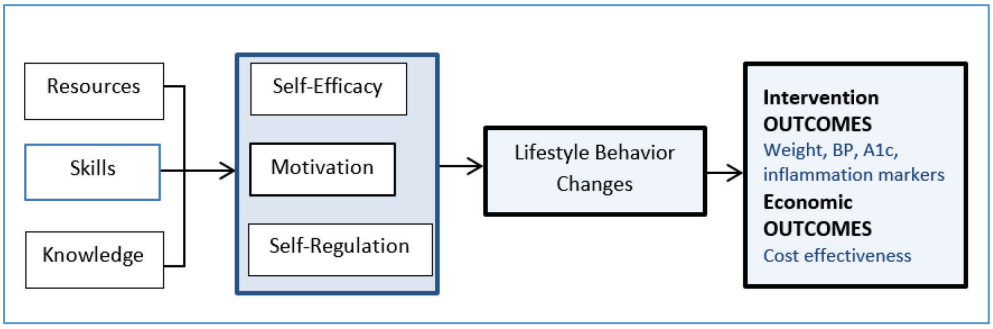
As depicted by the study flow diagram (Section 1.2), the experimental intervention (Med-South Weight Loss Program) is given in 3 phases. In this section, we will outline the overall features of the intervention and modifications we plan to make to the previously tested intervention. However, only a detailed description of Phase I will be provided in this version of the protocol. That is because, as planned, we are still revising the Phase II and III interventions to be up-to-date and consistent with the literature. Phase II begins in July, 2020.

The enhanced usual care intervention (control arm of the RCT) will be WW™, both workshop and digital, for 2 years. We will encourage patients in this arm at the outset of the study. Once the information is given about stating WW™ and we are confident the participant knows how to access this program, we will not actively promote their participation in the program (our goal is to approximate what might happen if a PCP refers a patient to WW™). As noted above, at measurement visits we will assess participation in WW™ and through a data use agreement, WW™ will provide us with process data. Information about WW™ can be accessed at the program's web site: https://www.weightwatchers.com/us/.

Description of the Med-South Weight Loss Program (note the text below is take from our research proposal and the proposal sub-headings have been maintained.)

3.3. Description of the intervention—the Med-South Weight Loss Program

Conceptual Model: The intervention conceptual model (see Fig.) combines constructs from cognitive and behavioral change theories. Our behavioral approaches are derived primarily from social cognitive theory (SCT),[83, 84] targeting self-efficacy, motivation, and self-regulation skills which have been identified as the best predictors of positive weight and physical activity outcomes.[85-87] To effect these predictors, the weight loss intervention, similar to other evidence-based programs,[88-92] incorporates techniques such as motivational counseling,[93] problem-solving,[94] self-monitoring, goal-setting, and cognitive (acceptance and commitment) strategies to address challenges to self-regulation of diet and physical activity.[95] In addition, food-related and socioeconomic barriers to lifestyle behavior changes will be assessed and addressed in intervention content. At the patient level, our model also recognizes the importance of dietary pattern as a key contributor to long-term intervention success. In the Women's Health Initiative RCT, most participants could not achieve and maintain the very low-fat diet that was recommended.[17] However, in the PREDIMED RCT, the higher fat, Med-style diets were maintained by study participants for the duration of the RCT.[96]



Overview: The Heart Healthy Lenoir weight loss intervention described below in ital. will be refined for this study.[75] The intervention is given in 3 phases as outlined in Fig 2. Below, we first outline intervention adaptations to enhance weight loss by phase and then across phases. In Sec. 3.4d we

describe enhancements for intervention implementation, which are relevant to future dissemination if the intervention is shown to be effective.

***3.1b. Preliminary data directly related to this application--Heart Healthy Lenoir (HHL) lifestyle and weight loss study**: This study (Keyserling, PI)[74, 97] integrated weight loss components from the studies described above with a previously tested lifestyle intervention[98, 99] to create the intervention that will be refined and tested in this proposed study. With funding from NHLBI as part of the Centers for Population Health and Health Disparities (Ammerman, overall PI),[100] this study enrolled 339 participants. All received an initial 4 month lifestyle intervention (Phase I), after which, those with a BMI > 25 kg/m^2 desiring weight loss (N = 138) enrolled in the weight loss intervention (Phase II) offered in 2 formats: 16 weekly group sessions (n = 57) or combination of 5 group sessions and 10 phone calls (n = 81). From 12 to 24 months (Phase III), both weight loss groups received a telephone-administered maintenance intervention. After Phase I, those who did not take part in the weight loss intervention continued with the lifestyle intervention which consisted of phone follow-up every 3-4 months. The dietary pattern advocated across all phases was very similar to the nut intervention arm tested in the PREDIMED RCT,[21] hence, we call it the **Med-South diet**. (Educational materials included in supplement to major outcomes paper.[74]) The PREDIMED intervention diets[21] included 13 major recommendations. In Table 1 (see page above), we list these and show that **9 of the 13 are virtually identical** to those tested in the Med-South diet in HHL. Importantly, we adapted the Med-South diet to include foods familiar to and affordable for residents of the Southeast (and more generally, the US), such as peanuts and peanut butter (same heart health quality as tree nuts[101]) as part of the recommendation to eat nuts ≥ 3 times a week and full-fat salad dressing as familiar foods with high-quality fats. Further, our adapted recipes for traditional southern foods, such as BBQ[102] and hush puppies,[102] were well-received by participants.*

Table 1: Comparison of PREDIMED to Med-South Dietary Goals*

Food	PREDIMED Diet Goal	Med-South Diet Goal*
1--Vegetable Oil	Olive oil group: ≥ 4 tbsp/day extra virgin olive oil	2-6 servings/day of foods high in healthy fats (nuts, fish, full fat salad dressings and spreads, foods prepared with olive or other vegetable oils, and vegetables with high fat content such as avocado)
2--Tree nuts and peanuts	Nut group: ≥ 3 servings/wk[b]	≥ 3 servings/wk
3--Fresh fruits	≥ 3 servings/day	≥ 7 servings for fruits and vegetables/day
4--Vegetables	≥ 3 servings/day	
5--Fish (especially fatty fish), seafood	≥ 3 servings/wk	≥ 1 servings/wk
6--Legumes	≥ 3 servings/wk	≥ 3 servings/wk
7--Sofrito	≥ 2 servings/wk	No recommendation
8--White meat	Instead of red meat	Consume poultry often
9--Wine with meals (optional, only for habitual drinkers)	≥7 glasses/wk	Do not recommend starting wine consumption; for those who drink, 1 serving a day for females and up to 2 for males
10--Soda drinks	<1 drink/day	<1 drink/day
11--Commercial bakery goods/sweets/ pastries	<3 servings/wk	<3 servings/wk
12--Spread fats	<1 serving/day	Up to several servings/day of trans fat free spreads
13—Red/processed meats	<1 serving/day	≤ 1 serving/day

* Blue accented rows indicate identical (or almost) recommendations to PREDIMED

We have recently reported weight loss outcomes (Table 2) through 24 months for those with diabetes (n=124) who took part in HHL.[75] (As noted in Sec. 3.3d, we expect greater weight loss in this study.)

Table 2: Weight and change in weight (% change) at 12 and 24 month follow-up for HHL Participants with Diabetes						
	12 Month Weight Outcomes			*24 Month Outcomes*		
Intervention Format	*N*	*Baseline Wt.*	*% Change (95% CI)*	*N*	*Baseline Wt.*	*% Change (95% CI)*
--with diabetes, group weight loss	*17*	*108*	*-3.6 (-6.9 to -0.4)*	*18*	*109*	*-4.8 (-8.8 to -0.7)*
--with diabetes, combo weight loss	*27*	*110*	*-2.6 (-5.0 to -0.2)*	*25*	*108*	*-2.0 (-4.3 to 0.1)*
--with diabetes, lifestyle only	*52*	*100*	*-0.2 (-2.0 to 1.6)*	*50*	*101*	*-3.8 (-5.9 to -1.8)*

Overall, among participants with diabetes, the mean percent weight change at 24 months was -3.6% (-5.0 to -2.0). In addition, 33% of participants with diabetes maintained 5% weight loss and 20% maintained 7.5% weight loss at 24 months. Ninety percent of those in the weight loss program were satisfied or very satisfied with the program. Importantly, among those in the lifestyle only group, weight loss was -3.8 kg (-5.9 to -1.8) at 24 months, suggesting a change in dietary pattern may have led to weight loss[75] without an explicit intervention to lose weight. A possible explanation for weight loss in this group, as compared to PREDIMED participants who on average lost minimal weight,[48] is difference in baseline diet, with more poor quality carbohydrates and processed food in the American diet compared to the European diet [103] and particularly so in the southeastern United States.[104-107] In this setting of excess poor quality carbohydrate intake, a change to a Med-style, unrestricted high-quality fat diet may have positive metabolic and appetite suppressing effects.[62, 63, 65] A major limitation of HHL weight loss outcomes was the pre-post study design, though weight loss over time is not commonly observed for adults and there were no secular trends suggesting weight loss in NC during the time of this study.[108] Also, the weight loss trajectory among participants with diabetes in HHL was different from most weight loss studies—weight loss improved over time, instead of the usual rapid weight loss over 6 months with attenuation of weight loss typically seen at 12 and 24 months.[109] This trajectory of weight loss may be clinically important in light of increased CVD risk reported for those with weight fluctuations.[110]

Among participants without diabetes in HHL, weight loss was 0.4 kg (-1.4, 0.6) at 24 months. There are several reasons why those without diabetes may have had less weight loss. On average, they weighed 8 kg (103 vs. 95) less at baseline[75] and the majority (54%) did not choose to be in the weight loss intervention. Thus, they may have had a lower level of motivation to lose weight than those with diabetes. Furthermore, both short- and long-term weight loss has been shown to be greater when the trigger for weight loss is medical in nature.[111]

3.3a. Phase I (4 months), lifestyle phase:

Behavioral content enhancements: We will enhance the initial 4 month lifestyle phase with additional content that focuses on preparing participants for the weight loss intervention in Phase II by introducing a set of stability skills shown to improve long-term weight management.[112] Proposed stability skills enhancements include: 1) learning how to eat healthfully without feeling deprived or dissatisfied; 2) becoming comfortable with frequent self-weighing (making peace with the scale); and 3) navigating inevitable disruptions.[112] However, there is still no expectation for weight loss during this phase.

Dietary composition enhancements/rationale: The tested Med-South program recommended frequent consumption of vegetable oils (including olive oil, but not specifically recommending olive oil) and nuts, including peanuts.[113] Given the benefits of extra virgin olive oil as demonstrated in PREDIMED,[21] we will encourage consumption of extra virgin olive oil for those who like the taste and can afford it. However, the intervention will continue to recommend consumption of low cost and familiar oils such as soybean,

peanut, and canola oil, as the scientific data supporting the positive health effects of vegetable oils with high polyunsaturated fatty acids (PUFAs) content are compelling,[114-116] including a beneficial effect of omega 6 PUFAs on CVD and total mortality.[38] Our rationale for recommending fish ≥ 1 serving per week vs. ≥3 servings is 1) cost-related, as fish can be expensive, and 2) scientific, as most of the benefit from fish consumption is realized with 1 serving per week.[117] PREDIMED limited spread fats to < 1 serving per week, but now that non trans-fat tub margarines are available with high-quality fat content (e.g., Smart Balance™ and others), we recommend consumption of high-quality spreads. As sofrito sauce is not commonly consumed in the US, we are not recommending it, but instead, familiar foods made with tomatoes, onions, and garlic such as salsa.

Of note, the proposed modified Med-South dietary recommendations are consistent with 1) the recently updated guidelines (2018)[118] from the American Diabetes Association, which recognize the merits of a Med-style dietary pattern, and 2) USDA Dietary Guidelines 2015-2020.[119] Given commercialization of the American food environment (chain restaurants/processed foods), food consumption patterns are similar across the country; thus, the Med-South dietary approach is likely an appropriate intervention for most of the US.

3.3b. Phase II (next 8 months), weight loss: The proposed behavioral weight loss intervention builds on the HHL weight loss program (Sec. 3.1b, see above)**.**

Weight loss enhancements: To improve short- and long-term outcomes, recent research supports the integration of additional cognitive components into the cognitive-behavioral treatment of obesity.[95, 120-122] These cognitive approaches, which include skills in mindful eating, acceptance of cravings and behavioral fatigue, behavioral commitment to clearly-defined values, and increasing awareness of how internal and external cues motivate eating decisions,[95, 120-122] will be incorporated into the content of the weight loss intervention. In addition, 3 key modifications are proposed to enhance the implementation of an adapted-HHL intervention delivered in a primary care setting. These modifications include: 1) an extended weight loss period (increased from 6 to 8 months); 2) individual contacts only (in-person and by phone); and 3) early identification of non-responders with optional stepped up care. The extended weight loss period of 8 months (2 months longer than standard 6-month treatment duration) is largely based on the desire to allow more time for weight loss and a 12-month measurement interval from baseline. With this longer weight loss period, participants may also benefit from additional intervention contacts. Delivery by individual contacts (without group-based format as an option) is an adaptation based on: 1) contextual factors (e.g., poor patient uptake of group programs, time needed to train and supervise group facilitators, and logistical challenges) that could negatively impact group-based delivery in primary care settings,[79] and 2) advantages of individual contacts and evidence of comparable weight loss outcomes in group vs. individual treatment delivery.[3, 80] With this change, intervention delivery is made easier for staff in primary care settings, provides the advantage of a closer relationship between participant and interventionist, and allows tailoring of the intervention to fit the needs of individual participants. New research[123, 124] guides our decision to identify non-responders early and then adapting the intervention to fit the needs of the individual. With this modification, we can step-up care for those participants who need additional contacts while maintaining the standard treatment for "responders."

3.3c. Phase III (next 12 months), long-term weight loss and maintenance of weights loss: The 12 month (Phase III) follow-up period provides an opportunity to determine weight loss maintenance success and weight change after the initial weight loss period. Weight loss maintenance following intentional weight loss remains challenging[125-127] mainly due to poor adherence to behavioral strategies and "physiological adaptations that promote weight regain."[128] Extending treatment following intense

weight loss programs can produce maintenance of an additional 3.2 kg of weight loss over 18 months, compared with no-treatment controls.[125]

Weight loss enhancements: We will build on strategies proven effective in our own studies and in other published research, while being cognizant of primary care setting contextual factors. Based on a review of the current evidence, extended care using personal contacts showed greater effectiveness in weight loss maintenance than technology-based interventions.[129] Some of the more effective weight loss maintenance interventions[130-132] have used phone counseling,[133, 134] and/or in-person contacts, generally delivered on a monthly basis. Our program includes monthly phone contacts with the option of biweekly contacts depending on individuals' progress. Adapting the number of contacts to match individual responsiveness is an important modification that addresses individual variability as a behavioral challenge to weight loss maintenance.

3.3d. Intervention enhancements across all phases
Dietary composition: In recognition that dietary composition impacts energy expenditure during weight loss maintenance (Sec. 1.2d) with low-glycemic and low-carbohydrate dietary patterns associated with improved maintenance of weight loss,[63,64] we will update our materials on carbohydrate recommendations to emphasize even more the importance of 1) regularly consuming lower glycemic fruits, less starchy vegetables, and whole grains and 2) reduced intake of their starchy/refined counterparts.

With these enhancements, we anticipate mean weight loss of ≥ 5% body weight at 24 month follow-up.

3.3e. Physical activity (PA) component. In HHL, we devoted about 25% of counseling time to an individually tailored, goal-oriented PA intervention advocating increased moderate intensity PA and decreased sitting time.[74] For this proposed explanatory trial with a primary focuses on dietary pattern and weight loss, we do not propose a high intensity PA intervention component. Instead, we will periodically mention PA recommendations consistent with national guidelines,[135] but no structured counseling is planned for PA behaviors. We anticipate PA will be roughly the same in intervention arms; however, we will carefully measure self-reported PA so we can control in our analysis for observed differences between groups, if present. We will ask participants to report their physical activity, particularly walking. We will assist participants in tracking their steps with use of a smart phone and will provide a pedometer to those without a smart phone for this purpose.

6.1.2 ADMINISTRATION AND/OR DOSING

Logistics of giving the Med-South Weight Loss Program

- The intervention will be given by trained research staff.
- For participants recruited from the Chapel Hill catchment area, the intervention will be delivered in person and by phone:
    - In person, face-to-face counseling visits, will be given at the UNC Center for Health Promotion and Disease Prevention, located at 1700 Martin Luther King, Jr BLVD, Chapel Hill, NC 27599. A minimum of 4 in-person counseling visits will be delivered at this location (first visit of Phase I, first visit of Phase II, 2 month follow-up visit of Phase II, and first visit of Phase III).
    - The other visits may be given in person or by phone. The phone counseling sessions may be supplemented with use of shared screen technology (e.g., Zoom™ session)

- The location of our counseling sessions in Eastern North Carolina is to be determined and will included in a further version of the protocol. (Enrollment visits in eastern North Carolina will start no later than April, 2021.)
- We will encourage participants to take part in all sessions. However, a participant will not be dropped from the study based on session participation. In the extreme, we will invite participants back for measurement visit even if they did not participate in any intervention counseling sessions.
- If a participant takes part in 70% or more of anticipated visits, we will consider this a "full-dose."
- The intervention format for this study is individual; there will be no group sessions or activities.

Description of Intervention for Phase 1

Phase I – Lifestyle Intervention: The content for this phase is currently available at: *http://hpdp.unc.edu/research/medsouth/med-south-materials/*. As outlined below under Phase I modifications, we will adapt the current physical activity intervention so that 1) it is less intensive than previously tested by our group and 2) approximates what we anticipate to be the physical activity recommendations in the augmented control group. Our goal in doing so is to isolate the dietary pattern as the primary behavioral intervention evaluated in this study.

Session Content and Delivery**:** The following content is addressed during the 4 major counseling session:

- Session 1: Nuts, Dressings, and Oils
- Session 2: Vegetables, Fruit, Whole Grains, and Beans.
- Session 3: Drinks, Desserts, Snacks, Eating Out, and Salt
- Session 4: Fish, Meat, Poultry, Dairy, and Eggs

At the first session, an overview of the program is given, an assessment of dietary behaviors relevant to session content is administered, and then the specific dietary content for Session 1 is presented. At the end of the session, the participant and counselor developed an individually tailored action plan to help guide the participant's eating behaviors for the next month (or until the next counseling session). To do so, they first review the assessment page for Session 1 and identify current eating behaviors that "could be improved" (middle column) or "need to be improved" (right most column) of assessment page. (In the Web-based version, problematic eating behaviors are presented according to an algorithm that prioritizes behaviors most in need of modification to improve CVD risk and counseling is organized as described for the paper version in this section.) Then they review the dietary tips for these problematic eating behaviors on the tip sheet for Section 1 with tips linked by number and color coding to the items on the assessment page. Of note, the tip sheet includes recipe suggestions in a "Southern Style" cookbook given to all participants. Finally, the counselor and participant identify 2 achievable goals (participants can opt to choose 1) to work on before the next visit and document them on the goal sheet. Subsequent sessions follow the same format but open with a check-in on progress toward goals and address diet and physical activity.

Approximately 1 week after the counseling sessions outline above, there is a follow-up phone call. During this phone call, the counselor will check on goals and 1) offer reinforcement for success in achieving goals or 2) problem solved issues related to lack of success in achieving goals. If the latter is

the case, the counselor and participants may collaboratively selected new goals to focus on before the next session. We anticipate these phone calls will last 10-15 minutes.

Phase I Enhancements/Modifications: In addition to the behavioral components already integrated into the lifestyle intervention, we propose to add a small set of cognitive skills that have been shown to improve weight loss maintenance, even without continued program contacts.[112] These skills increase intrinsic motivation to engage in lifestyle and self-regulation behaviors. Some of these 'stability skills' were included in our prior weight loss research, but not in the initial lifestyle phase. The table below (based on the Kiernan study[112]) includes a brief summary of 4 stability skills and examples of activities/discussions that will be integrated into the 4 monthly sessions.

Stability Skills	**Skill-Building Activities / Discussions**
□ Learning how to eat healthfully without feeling deprived or dissatisfied	○ Reduce comparisons between 'healthy vs. less healthy foods' (to lower perceived deprivation) ○ Find tasty replacements for foods that should be limited in frequency and quantity
□ Becoming comfortable with frequent self-weighing (making peace with the scale)	○ Weigh daily, track weight, and observe fluctuations to identify personal range ○ Practice interpreting weight fluctuations (gains) with calm, relaxed awareness and fine-tuning/adjustments
□ Making quick and easy adjustments to stabilize weight	○ Making small adjustments without keeping food/activity records ○ Eating (savoring and enjoying food) mindfully
□ Navigating inevitable disruptions	○ Recognize that disruptions are to be expected ○ Practice navigating high-calorie meals (e.g., Sunday family gatherings, vacations)
Other Cognitive and Behavioral Skills (based on principles and techniques of Cognitive Behavioral and Acceptance Commitment Therapy)	
□ Cognitive Behavioral Skills: Motivation, Self-Compassion, Distorted Thinking, Cognitive Restructuring, Positive Thinking, Emotional and Situational Triggers, Problem-solving, etc.	
□ Acceptance-Based Skills: Commitment to Behavior Change, Distress-Tolerance Skills, Mindful Awareness (eating behaviors)	

For this proposed explanatory trial with a primary focuses on dietary pattern and weight loss, we do not propose a high intensity physical activity intervention component. Instead, we will periodically mention physical activity recommendations consistent with national guidelines, but no structured counseling is planned for PA behaviors.

Phase II – Behavioral Weight Loss Intervention:

PHASE II WEIGHT LOSS PROGRAM (8 MONTHS)

Overview: The weight loss program for this study builds on our previously successful weight loss programs,[1-5] especially the Heart Healthy Lenoir Project.[3, 5] Refinements for this program include:

- Dietary factors: Research into macronutrient composition of meals, meal timing, and satiety and fullness, and partial use of portion-controlled meals are among the dietary factors we incorporate into the intervention for personalizing the approach to weight loss and especially for early non-responders
- Cognitive and Behavioral strategies: Principles of cognitive behavioral therapy (CBT), acceptance commitment therapy (ACT), and mindfulness are integrated into the refined program content.

Planned sessions as outlined in consent form:

Phase II	• 14 core sessions: the first and a visit about 2 months later must be in-person; choice of in-person or phone for all others. • 6-12 follow-up phone calls	• Core session (in-person) = 45-60 min. • Core session (phone) = 30-45 min. • Follow-up call = 20-30 min.	8.7 – 14 hours (core) 4.7 – 9.5 hours (Follow-up)

More detail on sessions and adaptive approach. As outlined in the table below:

- The first 8 core sessions are given weekly with the first in-person.
- The next 6 core sessions are given monthly, with 1-2 shorter follow-up phone calls given between sessions.
- Adaptive approach: Non-responders will be identified at 2 months and the intervention adapted to address the factors contributing to non-response. Limit to number of contacts in last 6 months is **maximum of 2 monthly phone follow-up contacts** added to the core monthly session.
- Note: Phase II Weight Loss Program content (*sequence* in which content is covered) may be adapted to meet the needs of individual participants. **Each session includes conversations specific to dietary behaviors, the Med-South eating pattern, and weight loss progress**

Session	Core Session Content
Week 1*	In-person visit required (4M Data Collection visit). ▪ Review of weight loss phase and study **weight loss goal**** ▪ Self-monitoring strategies (focus on self-weighing and food intake) ▪ Estimated energy needs + caloric restriction for modest weight loss ▪ Weight loss and diabetes and high blood pressure (safety recommendations for those on medication for diabetes and/or blood pressure) ▪ PA recommendations for weight loss
Week 2	▪ Med-South weight loss – personal meal planning (macronutrient composition match to adherence; timing of meals, etc.) ▪ Values, commitment, and behaviors ▪ Planning, food purchasing and meal prep

Week 3	• Social support communication • Food, fullness, and satiety • Revisit **Breakfast** meal • *Additional resource: whole grains and fiber (Manual pg. 25)*
Week 4	• Stress management • Emotional Eating • Revisit **Lunch** meal • Additional resource: meal prepping (Manual pg. 76)
Week 5	• **Personal Feedback Report** • Managing thoughts • Revisit **Dinner** meal
Week 6	• Time management and values • Revisit **Snacks** • Mindful eating – Part 1 • *Additional resources: Desserts, sweets, and snacks (Manual pg. 42), Kitchen Tips and Tricks (Manual pg. 75)*
Week 7	• Control and acceptance • Problem-solving skills
Week 8	• Eating out, Special occasions • Hunger cues • *Additional resource: Eating out and strategies (Manual pg. 44)*
Monthly contacts with 1 - 2 follow-up phone contacts (Months 3-8)	
Session 9* + f/u contact	In-person visit (required for non-responders) • **Personal feedback report** • Adapted weight loss approach based on personal factors (dietary and behavioral) • Eating pattern review and adjustments (meal timing, size, etc.)
Session 10 + f/u contact	• Mindfulness -Part 2 • Overeating triggers
Session 11 + f/u contact	• Revisit self-monitoring • Distorted thinking
Session 12 + f/u contact	• **Personal feedback report (6M)** • Adaptations to weight loss approach based on personal factors • Revisit Motivation
Session 13 + f/u contact	• Rewards and Affirmations • Relapse prevention • Weight loss maintenance

Session 14 **+ f/u contact**	▪ Support for weight loss maintenance ▪ Study WLM goals (review) ▪ Visioning 24 months out

*In-person visit required

To-achieve a **5% weight loss at 24 months, we need to account for at least a 1-3% weight regain. Thus our aim is for about **7% weight loss** goal by 12 months (end of Phase 11 weight loss program).

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Phase III – Continued Weight Loss and Maintenance of Weight Loss:

Phase 3 of DELISH counseling (Maintenance) prioritized three in-person visits (start of year 2, the 18-month halfway point, and the final visit at the 24-month end point) to educate the participants on weight-loss maintenance and how to continue with their goals once the intervention ended. In between these in-person counseling and measurement sessions, counselors provided monthly counseling sessions via phone as needed for each participant. Additional in-between phone call check-ins were available if requested by the participant. These sessions, both monthly and in-between calls, were more flexible and allowed the participants to choose which materials and educational handouts they wanted to focus on before finishing the intervention. This individualized counseling approach allowed for specialization of each participant's interests and needs as they finished up the intervention.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

We will assess fidelity in intervention delivery as follows:

- Enhanced usual care (WW™):
    - Per our data use agreement, WW™ has agreed to provide the study with the following process data: number of workshops attended (including dates of visits), workshop weights (if available), number of website or phone app logins (including dates and duration if available), and participant reported dietary and physical activity data.
    - At all study follow-up measurement visits (4, 12, and 24 months), research staff will carefully assess number, type, and duration of weight loss counseling sessions complete as part of the WW™ program.
- Med-South Weight Loss Program: We will assess fidelity of intervention delivery through multiple channels as describe below.
    - All counseling sessions will be logged into our REDCap data management program, including date and duration of visit.
    - After each visit, the counselor completes a checklist to indicate the components of counseling that were covered during the visit.
    - Audio recordings of up to 20% of sessions will be conducted during the 2-year period.
        - During Phase I and the early part of Phase II (first 2 months) a random 50% of the recorded counseling sessions will be reviewed and feedback provided to counselors. Recordings will be reviewed by study staff using a checklist to assess planned counseling components (accuracy of content covered and quality of delivery). If we find delivery fidelity is less than 80% of anticipated based on successful completion of counseling components, then the frequency of providing feedback to counselors from reviewed audio recordings will increase to ensure that the delivery fidelity goal has been achieved.
        - During the latter part of Phase II (last 6 months) and Phase III, audio recording will drop to 10% of visits (with review of up to 50% of recorded sessions), unless delivery fidelity is not achieved, in which the proportion reviewed will be increased to document achievement of fidelity goals.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization

This is an open-label, randomized controlled trial of 360 participants desiring weight loss and followed over 24 months. Participants will be randomized 1:1, stratified by practice and diabetes status, to either:

- Group 1: Med-South Weight Loss Program (the intervention);
- Group 2: WW™ (Augmented usual care).

Randomized assignment will be done by using the randomization function in REDCap stratifying on site and diabetes status and using randomly permuted blocks of random sizes for the randomization to achieve balance in the participant allocation.

Unblinding Plan

As an open-label study, participants, providers, and many study staff will know to which group individual participants have been randomized. The investigative team, MPIs and Co-Is, (excluding the study statisticians Daniela Sotres-Alvarez and David Couper) will be blinded to group assignment of any

aggregated outcome data available before the completion of all data collection. Drs. Sortres-Alvarez and Couper will not be blinded to study groups as their reports prepared for the DSMC will include unblinded data. Any key decisions by the study investigators (excluding the biostatisticians) regarding study outcomes, the appropriateness of test statistics or model assumptions, changes to this analysis plan, or any other statistical issues will be made in a masked review of the data (i.e., masked to the true randomization groups).

A randomization table (using randomly permuted blocks of random sizes for the randomization to achieve balance in the participant's allocation) will be prepared by the study statistician. This will be updated to the REDCap system by Drs. Sortres-Alvarez. Only study biostatisticians will have access to this table. Outcome datasets provided to the statistician by the data management team will include the randomized arm assignment. Other study investigators will not have access to the primary outcome data until all data have been collected.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Adherence to the intervention

- Twenty percent of counseling visits, selected at random, will be recorded and a subset of these reviewed to assess counselor adherence to the study protocol. In addition, the counselor will complete a brief questionnaire after each counseling session to record his/her observations about the process of the counseling session. This questionnaire will also be part of our assessment of fidelity.
- The extent to which participants perform weight management behavioral skills and cognitive strategies,[136] will be assessed from questionnaire data addressing self-monitoring of weighing, dietary behaviors, and goal-setting (instruments listed in the Measurement Table, Section 8.1.2).

6.5 CONCOMITANT THERAPY

Participation in this study does not preclude use of medications that are associated with weight loss. FDA approved weight loss medication will be allowed in both intervention and usual care groups, if recommended by the participant's clinician. Similarly, medications for diabetes associated with weight loss (SGLT2 inhibitors and GLP1 agonists) may be used during this study. We will specifically address use of these medications at all measurement visits. If an imbalance in use occurs across study groups, we will account for this in our sensitivity analyses.

Bariatric Surgery

At enrollment, we assess interest in bariatric surgery and if a potential participant is contemplating this within the next year, he/she will not be enrolled. That said, a patient may elect to have bariatric surgery at any time during his/her participation in this study. If a participant has bariatric surgery, he/she will be withdrawn from the study at that time. Data collected prior to withdrawal will be included in the analysis.

6.5.1 RESCUE THERAPY

No rescue therapy outside of the study protocol is planned if participants do not lose weight.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

The study intervention will not be discontinued unless the participant withdraws or is withdrawn as outlined in the above section.

If a participant withdraws or is withdrawn, no attempts will be made to collect follow-up measures.

If a participant requests to withdraw from the intervention but is willing to continue the measurement component of the study, he/she will be invited to continue with follow-up measures.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

Participants will be withdrawn according to protocol for the following reasons:

- New diagnosis of condition on study entry exclusion criteria list (type 1 diabetes and cancer, as defined on the list).
- Other medical diagnosis typically associated with significant weight loss (5% or more of body weight). In addition to malignancy, examples include nonmalignant gastrointestinal disease, endocrinopathies, infectious disease, rheumatologic diseases, etc. As Dr. Berkowitz (study Co-I, general internist) will be blinded to participants' study group assignment, he will adjudicate in these situations, seeking consultation from medical colleagues as appropriate.
- New diagnosis of cognitive decline confirmed by PCP as sufficient to interfere with insight related to food selection.
- New diagnosis of medical condition such that participation in a behavioral weight loss intervention is no longer appropriate.
- Permanent change in living situation (e.g. from home to nursing home) such that the participant has limited food options.

Pregnancy: Study participants who become pregnant may continue to participate in the study with the understanding that weight loss goals will be suspended during pregnancy through 3 months postpartum. If a pregnant participant wishes to continue with counseling session during pregnancy, the focus on counseling will be on dietary quality. The participant may resume full participation 3 months postpartum. Any data collected while the participant is pregnant will be censured and follow-up data will not be collected until the participant is 6 months postpartum.

A participant will be considered lost to follow-up if we are unable to contact him/her according to this algorithm.

- Attempts at telephone contact:

    - We will call up to 5 times over a 2 week period. We will attempt 2 calls during regular work hours (8:30 to 5:30 on weekdays) and 3 after hours, including Mon-Thurs evening between 5:31 and 9:00 pm and on Saturday calling between 8:30 and 5:30 pm.
    - We will leave up to 2 phone messages.
    - If no contact is made over this initial 2 week period as outlined above, we will undertake more limited contact attempts for an additional 2 weeks including up to 2 phone calls per week, 1 during business and the other during evening hours or on the weekend.
- Email: If a participant gives us permission to contact by email, we will send up to 4 weekly emails.
- Text: If a participant gives us permission to contact by text, we will send up to 4 weekly texts.
- Alternative contact: During enrollment, we will collect information on an alternative contact that we are given permission to contact. We will attempt to contact this individual up to 3 times a week for 4 weeks.

No replacement is planned for those who withdraw from the intervention for the study.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if we are unable to contact him/her according to this algorithm.

- Telephone contact:
    - We will call up to 5 times over a 2 week period. We will attempt 2 calls during regular work hours (8:30 to 5:30 on weekdays) and 3 after hours, including Mon-Thurs evening between 5:31 and 9:00 pm and on Saturday calling between 8:30 and 5:30 pm.
    - We will leave up to 2 phone messages.
    - If no contact is made over this initial 2 week period as outlined above, we will undertake more limited contact attempts for an additional 2 weeks including up to 2 phone calls per week, 1 during business and the other during evening hours or on the weekend.
- Email: If a participant gives us permission to contact by email, we will send up to 4 weekly emails.
- Text: If a participant gives us permission to contact by text, we will send up to 4 weekly texts.
- Alternative contact: During enrollment, we will collect information on an alternative contact that we are given permission to contact. We will attempt to contact this individual up to 3 times a week for 4 weeks.

If we are unable to contact a participant as outlined above, a letter will be sent to the current mailing address in the EHR outlining our attempts to contact the participant and inviting the participant to contact us if he/she still wishes to participate in this study.

Should the participant continue to be unreachable and does not respond to the mailed letter within 4 weeks, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

8.1.1: Screening, eligibility assessment, and consent

- Outlined in detail in Section 5.5, Strategies for Recruitment and Retention.

8.1.2: Overview of study measures

Study data will be collected at baseline, 4, 12, and 24 months. Process data for the intervention group (Med-South Weight Loss Program) will be collected as part of the intervention via the web-based platform and via REDCap questionnaires completed by counselors immediately after counseling sessions. Process data for the enhanced usual care group will be assessed via a Data Use Agreement with WW™ and by questionnaire at follow-up visits. *As recommended by NIH, our measures include ADOPT[137-139] core constructs (in blue) and specific instruments (in blue underlined) as noted in the Table.*

Primary and Secondary Aims 1 and 2:

Table 3: Outcomes/ Measures	Collection Time (min)	Data collected times (months)				Comment
		0	4	12	24	
Weight (primary outcome), by electronic scale as the average of two measures, and height (baseline only). SECA 874 dr scales will be used and assessed monthly for accuracy with standardized weights..	5	x	x	x	x	At study outset, seven standardized 50 lb. weights certified for accuracy by NC state standards lab.*
Secondary Outcomes						
Objective measures						
--Blood pressure by noninvasive automated monitor (Omron HEM-907XL, Vernon Hills, IL) with a first measure after seated for 5 minutes and 2 repeat measures at 1-minute intervals	10	x	x	x	x	
--Blood work: performed by LabCorp • Fasting lipid panel: total cholesterol, triglycerides, HDL, and calculated LDL and VLDL. If participants are unable to fast a non-fasting sample is collected with non-fasting stat noted • A1c • Other chemistry: glucose, ALT, creatinine (if not previously checked in prior 2 years and only at baseline), and CRP	10	x	x	x	x	Creatinine collected at baseline for those without measure in preceding 2 years.

--blood work: preformed in lab of Dr. Steve Hursting. Serum and plasm specimens are frozen to – 80 C. immediately after collection and processing. • interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, and C-reactive protein (C-RP)						
--*skin carotenoids, Reflection Spectroscopy Device ("Veggie Meter"™)*[140-142]	5	x	x	x	x	
Questionnaires:						These data collected before the actual visit, on-line via REDCap or by phone. Window before baseline visit is 4 weeks. Window before follow-up and after follow-up visits is is 2 weeks.
--Demographics and medical history (baseline only)	15	x				
--Diet assessment: diet quality,[143] adapted PREDIMED checklist[19, 96]	10	x	x	x	x	
--Detailed assessment of diet quality: Willett Food Frequency Questionnaire[144]	20-30	x	x	x	x	
--Physical activity and sedentary behaviors: *GPAQ for physical activity and sedentary behavior,*[145] participant report of monitored steps	5	x	x	x	x	
--Quality of life (EQ5D[146])	5	x	x	x	x	
--Food insecurity[147]	2	x	x	x	x	
Diet Self-Efficacy Scale[148]	3	x	x	x	x	
Weight Loss Self-efficacy Short-Form (WEL-SF1)[149, 150]	3	x	x	x	x	
Early Self-Weighing Questionnaire[151]	1	x	x	x	x	
Self-Regulation: Dietary Self-Regulation (TSRQ)[152]	3	x	x	x	x	
Three-Factor Eating Questionnaire[153]	3	x	x	x	x	
Mindful Eating Questionnaire[154] **	5	x	x	x	x	

Perceived Stress Scale[155]	3	x	x	x	x	
PHQ-8[156]	3	x	x	x	x	
--Medications for high BP, high blood lipids, diabetes, and weight loss (self-report with EHR review)	5	x	x	x	x	
--Adverse outcomes, CVD events, ER visits, and hospitalizations (follow-up only)	5		x	x	x	
--Acceptability (follow-up only)	5-10		x	x	x	
Diet and PA goals and success achieving goals (collected by web-based intervention platform and counselor)	NA					Collected after each counseling session in intervention group.
Exploratory Outcome						
Stool microbiome (participants may elect not to complete this measure)	NA	x	x	x	x	First sample will be collected in the 2 week period immediately after randomization. (These are the only baseline data collected after randomization.) The follow-up samples will be collected w/n a 2 week window of follow-up visit date.
Other						
--EHR to assess/confirm adverse health outcomes	NA		x	x	x	To confirm information collected by questionnaire at these visit time points

***** http://www.ncagr.gov/standard/Labs/

**Added to baseline on 12/22/20. No follow-up data had been collected at this point in the study.

Note: table last updated 3/1/21

Additional Study measures—economic outcomes

The budgetary impact assessment and numerator for the cost effectiveness analysis will be based on Activity Based Costing Questionnaires previously developed and applied by Dr. Finkelstein in similar studies[99, 157] along with participants' health care claims data that will be used to compare resource

utilization between the intervention and control groups. The denominator for the cost effectiveness analysis will focus on weight loss (kg) and health related quality of life as assessed using the EQ-5D-5L.[146]

8.1.3: Detailed protocol for data collection

8.1.3a: Protocol Updated 3/16/21: Study visits after hospitalization.

- Enrollment and follow-up measurement visits:
    - May occur 2 or more weeks after hospital stay if less than 7 days (defined as 2-7 nights in the hospital).
    - May occur 30 or more days after hospital stay of more than 7 days (defined as 8 or more nights in the hospital).
    - Note: ER visits and 1 night in the hospital (often defined as observation) do not count as hospitalization.
- Counseling sessions:
    - No interval specified. To be determined by counselor and participant.

Note: Research staff will be trained and periodically retrained on data collection protocols. Baseline training will include detailed review of and practice with protocols under the direction of the study's MPIs, Study Manager, and Data Manager. Retraining will occur at quarterly intervals.

8.1.3.1: Weight and height protocols

- At study outset, weights (seven 50 pound weights) assessed and adjusted for accuracy on 12/3/19 by North Carolina Department of Agriculture and Consumer Services Standards Laboratory.
- Weights to be re-assessed and adjusted for accuracy annually.
- Scales tested for accuracy the first week of each month during their use in this study.

Seca 874 dr Scale Tolerance Testing

(updated 1/28/20)

The scale's 6 AA batteries should be replaced at least once a year.

It is **imperative** that tolerance weights be handled carefully (no slamming around or banging against one another) to maintain their accuracy.

Before starting the test set the **ON-OFF** switch to **ON.** Press the **start** key with no load on the scale. If necessary switch the weight display from **kg** to **lbs** by pressing the **2 in 1** key for approximately 3 seconds.

1) Place a 50 lb wt in the center of the scale and record weight. (~50 lbs) Remove the 50 lb wt. Press **start** key.

2) Carefully stack two 50 lb wts on top of one another in the center of the scale. The first weight must be gently vibrated until the second is in place to prevent the scale from prematurely locking in and giving an erroneous reading. Record the weight reading (~ 100 lbs). Press the **2 in 1** key.

3) Place a third 50 lb wt on the scale and record weight. (~50 lbs The sum of this weight and the weight observed in step 2, ~ 100 lbs, is the observed reading for the expected weight of 150 lbs) **Remove the top 50 lb wt. only**.

4) Place two 50 lb wts on top of the two remaining weights vibrating the stack as before. Record the weight reading (~ 100 lbs The sum of this weight and the weight observed in step 2, ~ 100 lbs, is the observed reading for the expected weight of 200 lbs). Remove all four weights. Press **start** key.

5) Carefully, but quickly, stack five 50 lb wts on top of one another in the center of the scale, gently but firmly vibrating the stack until the fifth weight is added. Record the weight reading (~ 250 lbs). Press the **2 in 1** key.

6) Place a sixth 50 lb wt on the scale and record weight. (~50 lbs The sum of this weight and the weight observed in step 6, ~ 250 lbs, is the observed reading for the expected weight of 300 lbs) **Remove the top 50 lb wt. only**.

7) Place two 50 lb wts on top of the five remaining weights vibrating the stack as before. Record the weight reading (~ 100 lbs The sum of this weight and the weight observed in step 6, ~ 250 lbs, is the observed reading for the expected weight of 350 lbs). Remove all weights.

8) Set **ON-OFF** switch to **OFF.**

During the testing if any observed reading falls outside the tolerance range repeat the testing steps to verify the reading. No need to continue testing the scale if a weight is out of range and verified. Scales failing the tolerance testing should no longer be used.

lbs	**0.40% Tolerance Limit**	**Range**
50	0.2	49.8 - 50.2
100	0.4	99.6 - 100.4
150	0.6	149.4 – 150.6
200	0.8	199.2 – 200.8
250	1	249.0 – 251.0
300	1.2	298.8 – 301.2
350	1.4	348.6 – 351.4

Scale S/N _____

Date _____

Expected Weight (lbs.)	Observed Weight (lbs.)	Difference (lbs.)	0.40% Tolerance Limit (lbs.)
50			0.2
100			0.4
(50)			
150			0.6
(100)			
200			0.8
250			1
(50)			
300			1.2
(100)			
350			1.4

WEIGHT MEASUREMENT PROTOCOL

(last updated 10/28/19)

Prior to the appointment the participant is instructed to wear light clothing and informed that the weight measurements will be made with shoes removed.

Materials

- Seca model 874 dr electronic personal scale

Preparation

- Place the scale on a hard level surface.
- Turn the scale ON with the ON-OFF switch. Press the start key with no load on the scale. The scale is automatically set to zero and ready for use.
- Once the digital display reads zero **verify that "lbs" unit is showing**. If "kg" appears in the display press the 2 in 1 key for approximately 3 seconds. "lbs" should then show in the display.

Procedure

Participant

- With shoes removed, scale displaying zero; step onto the middle of the scale.
- Stand on both feet, knees extended (straight) with arms by sides.

Research Staff

- Once the reading in the digital display is stable, record the first weight on the Weight Measurement Form in lbs, **recording the tenths of lb** (i.e. 81.4 lbs).
- Have the participant step off the scale.
- Have the participant step back onto the scale once zero is displayed. **Note:** You may need to restart the scale by pressing the start key to obtain the zero and lbs display before instructing the participant to step back onto the scale.
- Once the reading in the digital display is stable, record the second weight on the form.
- Record the difference between the first and second readings.
- If the **difference is greater than 1 lb repeat** and record a third weight.
- When finished weighing participants turn the scale OFF with ON-OFF switch.

Note

- A stabilized reading in the scale display is needed for recording. The participant needs to stand very still while breathing naturally. If moving too much the weight will not stabilize in the display.

Scale Accuracy Testing

- To insure accuracy the scales have been tested using certified tolerance weights. (Performed by research center staff each month).
- Staff should weigh themselves whenever the scale is set up for participant measurement

Scale Care

- Treat the scale as a laptop. Do not bump against other objects or expose to extreme temperatures.
- Store in the horizontal position without stacking anything on top.
- Do not allow anyone to weigh without your supervision and instructions.
- When not using, turn the ON-OFF switch to OFF to conserve the battery.

8.1.3.2: Height Protocol

HEIGHT PROTOCOL

(last updated 1/28/20)

Prior to the appointment the participant is instructed to wear light clothing and informed that both height and weight measurements will be made with shoes off.

Materials

- Shorr infant/child/adult stadiometer

Procedure

Participant

- Shoes removed.
- Back to the height board, heels all the way to the back.
- Standing up straight with arms by sides (**Evaluate posture** to be sure participant is standing upright, flat-footed and looking straight ahead with head in the Frankfort horizontal plane, the horizontal plane which includes the lower margin of the bony orbit--the bony socket containing the eye--the most forward point in the supratragal notch--the notch just above the anterior cartilaginous projections of the external ear). See "Frankfort Plane for Measuring Body Height" diagram.

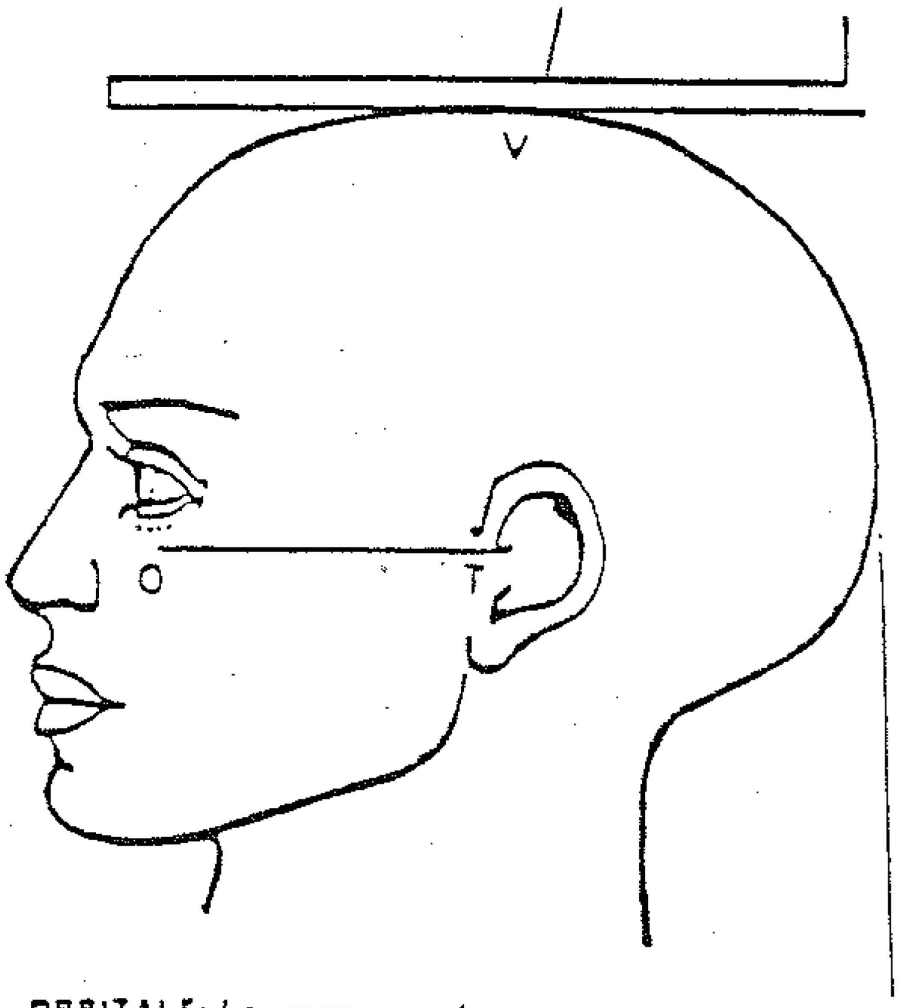
9 Research Staff

- Lower the sliding headpiece onto the participant's head.
- Read the measuring scale of the stadiometer to the **nearest 1/8th inch** (Note: stadiometer is scaled in inches, not centimeters).
- Two measures are taken and recorded on REDCap form. The participant steps off the stadiometer between measures. If the two measures **differ by >1/4 inch a third measure is taken** and recorded in the "blank" for the 3rd observation.
- Height is determined from the 2-3 observations (the average of the 2 closest measurements, **rounding up to nearest 1/8th inch**) and recorded on the form.
- Record your staff ID number on the REDcap form.

Notes:

- If the participant is breathing heavily enough to cause oscillations in the sliding headpiece, you must wait until s/he has settled down or ask to exhale and hold breath.
- If the participant's hairstyle interferes with measurement, be flexible and creative and get an accurate measurement (i.e. remove ponytail holders, measure hair height with tape measure, flatten hairdo, etc.).
- If the participant's buttocks cause an irregular or very unnatural posture when the heels are against the back of the board, allow standing with feet under hips (heels will not be against the back of the board in this case).

Frankfort Plane for Measuring Body Height



ORBITALE: Lower margin of eye socket

TRAGION: Notch above tragus of ear or at upper margin of zygomatic bone at that point

FRANKFORT PLANE: Orbitale tragion line horizontal

8.1.3.2: Blood pressure protocol

BLOOD PRESSURE PROTOCOL
(updated 1/28/20)

Warnings

- Do not share an electric outlet with another unit or electric appliance.
- Keep unit at least 5 feet from cell phones and computers.
- Unplug AC adaptor from electric outlet if unit is unused for an extended period of time.
- Do not inflate the cuff without being wrapped over the arm.
- Do not store unit under high temperature and high humidity.
- Transport the unit inside a car, not in the trunk.

Materials

- Omron Model HEM-907XL blood pressure monitor with small, medium, large, and extra large cuffs

- Tape measure

Note: The Omron cannot be used on arms with a circumference greater than 17" (large Omron cuff does not fit) or if the Omron is unable to take the measurement.

Procedure using the Omron
Set up

- Connect the AC adapter to the DC jack of the main unit and the electric outlet.
- Connect the air tube to the main unit by securing the air plug to the base of the air connector. This air tube is for use with the small, medium, and large cuffs only. The extra large cuff has its own non-detachable air tube for connection to the main unit.

Participant

- Should avoid caffeine, exercise, and smoking for at least 30 min before measurement.
- Invite participant to empty bladder before measurement .
- Shirt, blouse, or dress sleeves are loose fitting enough not to cause constriction of the arm even when pushed up for wrapping the cuff onto the bare arm. If too tight, the arm needs to be placed outside the sleeve.
- Remains quietly seated in a chair with both feet flat on the floor and back supported while measurements are taken. Neither the participant nor the staff should talk during the 5 min rest period or during the measurement.

Research Staff

- Apply the cuff to the right arm of the seated participant. **All BP measurements are made using the <u>right arm</u> unless prevented by injury or deformity.** If the left arm is used it is indicated on the BP and Heart Rate (BPHR) form and subsequent BP measures are taken using the left arm. See "How to Apply the Cuff" diagram.

- Measure the circumference of the largest part of the upper arm and select the cuff according to arm size.
    - 7”-9” small
    - 9”-13” medium
    - 13”-17” large
    - 17”- 20”extra large
- Connect the air tube and the cuff/bladder set by rotating the Luer connection.
- Place the participant’s hand with the palm upward.
- Align the Artery Position Mark on the cuff with the brachial artery.
- Wrap the cuff snugly using both hands and securely fasten it with the Velcro™ tape. The **lower edge of the cuff should be placed ½” to 1” above the inner side of the elbow joint**.
    - If the INDEX is positioned outside the RANGE, select the cuff suitable for the patient’s arm circumference and wrap it again. Wrap the cuff so that you can insert only one finger between the cuff and arm. If the upper arm is more pyramid shaped rather than cylinder shaped it is necessary to wrap the cuff in a slightly diagonal fashion so that both the upper and lower borders of the cuff fit snugly against the skin.
- Keep the **level of the cuff at the same level as the heart** during the measurement. The participant should sit upright in the chair, not slouching, with arm supported (eg, resting on a desk)..

- Take the blood pressure.
    - Push the ON/OFF (power) BUTTON to turn on the power.
    - Set the MODE Selector to “AVG”. The monitor has been programmed to:
        - Wait 5 min. until the 1st measurement.
        - Take 3 measurements.
        - Wait 1 min. between measurements.
    - Set the P-SET (inflation level setting) Knob to “AUTO”.
    - Push the HIDE button for non-display of results.
    - Push the START Button to begin measurement. The 5 minute countdown will be displayed. After 5 minutes the monitor takes the first measurement and then displays the results. One minute later the 2nd measurement is taken. The monitor takes the 3rd and final measurement after another minute.
        - To stop a measurement, push the STOP Button. The unit will rapidly deflate.
        - Do not push the START Button without first wrapping the cuff around the participant’s arm.
        - If an error occurs during measurement, the monitor will automatically start measurement again. If a second error occurs, measurement will automatically stop.
        - If the monitor determines that the pressure value is not correct, an error display appears (Er1 to 9). In this case, refer to Page 28 of the manual and start the measurement again.
        - **If the blood pressure is unattainable using the monitor the measure will be missing. <u>Note this on the form</u>** by checking appropriate option 1) arm circumference greater than 17” 2) Omron unable to measure.
    - Push the HIDE button for display of results.

- Enter measurement results on the form.
    - After all 3 measurements are completed; the average value will be displayed.

- Enter the average pulse rate (BPM) on the form.
- Press the DEFLATION (deflation control) /Measurement Result Display Switch Button to display the 1st measurement for entering.
- Press the same button again to display the 2nd measurement for entering.
- Press the button again to display the 3rd measurement for entering.

- Push the ON/OFF (power) Button to turn off the power.
- Mark right/left arm and record your staff ID number on the form.

Blood Pressure Feedback Card

- Fill in the date and the average of the 3 readings.
- Check a blank for recommendation if appropriate.
- Give to participant and point out any checked recommendation.
- If blood pressure is > 140/90 we will recommend the following:
- 140-159/90-99 [Check with your clinician within 2 months.]
- 160-179/100-109 [Check with your clinician within 1 month.]
- 180-219/110-129 [Check with your clinician within 1 week.] Also, staff will send Epic note to primary care clinician.
- Greater than 220/130 [Check with your clinician within 24 hours.] Also, staff will send Epic note to primary care clinician.
- *If the systolic and diastolic pressures are in different categories, follow the recommendations for the category with the shortest follow-up interval

8.1.3.3: Blood specimen collection protocol

Collection of Blood Specimens
(drafted 11/26/19)

This document outlines the lab protocols for this study. It is organized into 2 sections:

- Lab work that will done by a commercial laboratory and generally considered routine clinical lab tests
- Special research lab tests

Routine Clinical Labs Tests

- This lab work will be performed by LabCorp (Burlington, NC). As our negotiated pricing is favorable, we are able to do some additional testing not included in our NIH proposal, as outlined below.
- Lab measurement time points: baseline and 4, 12, and 24 months follow-up. Routine clinical lab tests will be collected at all time points, except for creatinine as noted below. *Note, in the proposal, non-fasting blood work was proposed, but we have modified the protocol to collect fasting blood work.*
- Lab tests to be done as outlined in the proposal
  - total cholesterol, HDL cholesterol, A1c, CRP, creatinine (on participants who do not have a creatinine in the medical record within the last 2 years, baseline only)
- Additional lab tests
  - Fasting glucose -- with the decision to collect a fasting sample, we might observe changes in fasting glucose and this test will allow for calculation of HOMA-IR

- Triglycerides -- with the decision to collect a fasting sample, we might observe changes in triglyceride levels and having triglycerides will allow us to calculate LDL.
- ALT – we will use as single lab test as a crude monitor of fatty liver

Test Collection and Sample Stability Information (as outlined on LabCorp website)

Test	Code	Tube	Preparation	Vol.	Temp	Stable
Total cholesterol	001065	Gel barrier	Separate serum or plasma from cells within 45 minutes of collection	.5 ml	room	14 days
HDL cholesterol	001925	As above	As above	.5 ml	Room	3 days
Triglycerides	001172	As above	As above	.5 ml	Room	7 days
Creatinine	001370	As above	As above	.5 ml	Room	14 days
Glucose	001032	As above	As above	.5 ml	Room	14 days
ALT	001545	As above	As above	.5 ml	Room	7 days
CRP	006627	As above	Not stated	1 ml	Room	14 days
A1c	001453	Lavender top	Not needed	4 ml stated; ped tube may be used	Room	14 days

Collection Protocol

- Participants will be asked to fast for 9 hours before blood collection. Liquids w/o calories are acceptable as is taking medication. Those with diabetes will be instructed to bring a snack with them in case they experience low blood glucose.
- If participant has not fasted for at least 9 hours, he/she will be re-scheduled for another time.
- The LabCorp requisition and 2 tube labels will already be filled out by study staff with the exception of SPECIMEN DATE and SPECIMEN TIME (Collection Date and Time for labels). These will need to be filled in by lab personnel. Note: lab for routine clinical lab tests will include identifying data including participants name and date. The report from LabCorp will be entered into the UNC electronic medical record as a scanned document. The specimens will be discarded according to the standard operating procedures of LabCorp.
- Lab personnel will need to fill in their first and last initials in the appropriate boxes for tubes collected on the LabCorp Specimen Collection form.
- **Using standard phlebotomy technique, collect:**
    - 8.5 cc SST (gel) tube (total cholesterol, HDL Cholesterol, triglycerides, glucose, ALT and creatinine). After collection:
        - Gently invert the gel-barrier tube 5 times to mix the clot activator and blood
        - Place the collection tube in the upright position in the rack, and allow the blood to clot at room temperature for 30 to 60 minutes (aim for 45 minutes). (Minimum clotting time is 30 minutes for patients with an intact clotting process.)
        - After allowing the clot to form, insert the tube in the centrifuge, stopper end up. Operate the centrifuge for 10 minutes at the speed recommended by the manufacturer. Prolonged centrifugation may cause hemolysis. Do **not** exceed 10 minutes of spin time unless otherwise specified.

        - Turn the centrifuge off, if not an automatic turn off, and allow it to come to a complete stop. Do **not** stop it by hand or brake. Remove the tube carefully without disturbing the contents. Inspect the barrier gel to ensure that it has formed a solid seal between the serum and packed cells.
        - It is not necessary to transfer serum to a plastic transport tube. Serum specimens may be sent at room temperature.
    - 3cc lavender-top tube (Hgb A1c)
        - No centrifugation needed.
    - Process as usual for LabCorp pick-up (samples do not need to be refrigerated)
        - Study research staff will notify LabCorp if courier does not stop by daily.

Special Research Labs Tests

- Special research tests to be performed as outlined in the proposal
    - Inflammation: IL-6, TNF-a, CRP (CRP will be done as part of the clinical lab work, as above)
- Additional research tests that may be done:
    - **Energy homeostasis:** adiponectin, leptin [could also consider amylin]
    - **Hunger/satiety:** Ghrelin – [could also consider Glucagon-like peptide (GLP)-1, PYY]
    - **Metabolic function:** insulin to assess insulin sensitivity (HOMA-IR, based on glucose and insulin level)

The collection protocol for blood specimens to be assessed for special research tests as outlined above requires freezing at -80 C. as promptly as possible. Within the Chapel Hill catchment area, which will include at least ½ of the study participants, plasma and serum specimens will be collected in a setting where collection time to placement in a -80 C. freezer will be approximately 20-30 minutes for plasma and 40 minutes for serum samples. Outside of the Chapel Hill catchment area, it may not be possible to collect specimens and move to cold storage in this time frame.

All participants in both catchment areas will have a sample collected to be stored for potential future DNA analysis.

Tubes will be pre-labelled. Tubes for cold storage will include PT ID#, date of collection, and first and last initial. Tubes for DNA collection will include PT ID#, date of collection, but **NO** initials.

Plasma Cold Storage: 6 cc green-top (sodium heparin) vacutainer for plasma

- Tap the tube gently to release additive adhering to the tube or stopper diaphragm. (See Figure.)

- Permit the vacuum tube to fill completely. Failure to fill the tube will cause an improper blood-to-anticoagulant ratio and yield questionable and/or QNS test results.

- To avoid clotting, mix the blood with the anticoagulant or preservative immediately after drawing each sample.
- To allow adequate mixing, slowly invert the tube eight to ten times using a gentle wrist rotation motion.
- Immediately centrifuge the specimen for 20 minutes (room temperature is acceptable). Do **not** remove the stopper.
- Turn the centrifuge off, if not an automatic turn off, and allow it to come to a complete stop. Do **not** stop it by hand or brake. Remove the tube carefully without disturbing the contents.
- Remove the stopper and carefully aspirate plasma, using a separate disposable Pasteur pipette for each tube.
- Place the tip of the pipette against the side of the tube, approximately ¼ inch above the cell layer. Do **not** disturb the cell layer or carry any cells over into the pipette. Do **not** pour off; use transfer pipette.
- Using the pipette transfer 1.5-1.75 ml plasma to each of two 2 ml cryovials, capping one with a YELLOW cap and one with a BLUE cap.
- Place in study storage box in -80 C. freezer according to color of vial cap. There will be a box for each color.

Serum Cold Storage: 8.5 cc SST (gel) tube

- Prepare using protocol for gel tube outlined above.
- Transfer 1.5-1.75 ml of serum to each of two 2 ml cryovials, capping one with a GREEN cap and one with a RED cap.
- Place in study storage box in -80 C. freezer according to color of vial cap. There will be a box for each color.

DNA: 10 cc PAXgene Blood DNA tube (collects 8.5 ml blood)

- Should be the last tube drawn in a series of tubes
  To guard against backflow:
  - Place participant's arm in a downward position
  - Hold tube with the stopper uppermost
  - Make sure tube additives do not touch stopper or end of the needle during venipuncture

- After collection gently invert the tube 8-10 times
- For locations with access to -80 C freezer. Place in box in Freezer.
- For locations without access to -80 freezer. Store tube upright at <u>room temperature</u>. Will ship every 2 weeks to Dr. Steve Hursting's lab for storage at -80 C.

Note: Transfer of specimens to Dr. Steve Hursting's lab at the UNC Gillings School of Public Health

- Specimens stored in cold freezers **with** generator backup will be transferred on dry ice to the Hursting lab approximately 2 **months**.
- Specimens stored in cold freezers **without** generator backup will be transferred on dry ice to the Hursting lab every 2 **weeks. Update 3-25-21:** Transfer may be up to every 6 weeks depending in part on number of specimens collected.

8.1.3.3a: Lab Protocol Update 3-25-21:

- **Protocol amended 9-17-20 re baseline phlebotomy.** If unable to get blood specimens on randomization day due to lack of success by phlebotomist and if participant agrees, will allow for return phlebotomy within 10 days.
- **Protocol amended 3-25-21 re blood work collection by UNC Phlebotomy**.
    - If study phlebotomist/staff unable to obtain blood after a minimum of 3 tries, participant may go to UNC phlebotomy lab for blood draw within 10 days, but preferably w/n 3 days. From campus site, there will be a 10-15 min delay in processing. From Eastown site, there will be about a 10 min delay in processing.
    - If study phlebotomist/staff are not available for a measurement visit, participant may stop by UNC lab to have study phlebotomy done before coming to study office for the measurement visit. The samples will be brought to the research office promptly for processing.

Protocol specification note 3-25-21. If we are unable to obtain baseline blood work, we will not attempt to obtain follow-up blood work. For 2 reasons: first, likelihood of success on follow-up may be low as "difficult stick" and second, no baseline for comparison.

8.1.3.4: Veggie meter protocol

Veggie Meter® (RS-Assessed Skin Carotenoid Device) Measurement Protocol
(updated 1/26/20)

Objective

Participant skin carotenoids will be assessed using a pressure-mediated reflection spectroscopy (RS) device (Veggie Meter®). RS uses broad-band white light to measure skin carotenoids directly through their respective absorptions from 400-750 nm. Reflected light is routed to a spectrograph coupled with a room-temperature detector array. The RS device measures finger skin tissue and adjusts for potentially confounding effects of melanin and hemoglobin. Participants will clean their hands with soap and water, the right index finger will be scanned 3 times and the average value will be used in our analysis. Each scan take ~3 seconds. Regarding RS cross-calibration to ensure comparability across the NC and MN sites, each RS Device comes with a standard calibration method that is used for all devices. In order to assess reliability (reproducibility of the measure), we will use the same strategy used in our small validity paper, [61] wherein RS measures are taken three times in the same person at the same time point, and we will calculate reliability.

To use the Veggie Meter®, the finger is inserted into the instrument's finger cradle to a) bring the pad of the fingertip in close contact with a light delivering and collecting contact lens, and b) to gently apply pressure to the finger such that blood is temporarily squeezed out of the measured skin region. A laptop computer interfaced to the instrument analyzes the light that is reflected from the finger, and subsequently derives a carotenoid score. The measurement takes 10 or 45 seconds, depending on whether a single- or multiple measurement mode is chosen, respectively. In multiple measurement mode, the finger is inserted and retracted three times and an average score is determined for the three measurements. In this study, we will use single-measurement mode, and will ask participants to insert and reinsert their fingers three times. Since carotenoid levels differ slightly between fingers, always measure the same finger when tracking changes. For this study's purposes, we will use the right index finger.

Veggie Meter® Supplies and Calibration

1. Supplies
    a. The Veggie Meter® consists of a box shaped base or pedestal that contains the electronics and an oval-shaped housing unit on top of the base that provides an optical interface for the fingertip to be measured (see Figure 4).
    b. Two cables (gray and black)
    c. Laptop
    d. Stopwatch
    e. Note that the Veggie Meter® is highly sensitive so avoid exposure to excessive heat and bright light.

Figure 4. Veggie Meter® Components

2. Device Calibration
    a. Prior to skin measurements, connect the two cables of the Veggie Meter® with the USB ports on the laptop. The gray cable from the base goes into the back port and the black cable from the housing goes into the front port. Note that the two USB ports are NOT interchangeable (see Figure 5).

Black and gray cables from

Black cable in front

Figure 5 Veggie Meter® Setup

b. Connect the laptop with the power outlet or run the Veggie Meter®/laptop system on battery for a few hours.
c. Power up the laptop by pressing and releasing the power button located above the keyboard on the right.
d. Tap on the mouse pad to activate user screen and enter password “project”.
e. Power on the Veggie Meter® by pressing the power button in the back of the instrument housing. There are two buttons. The power button is the bottom button that sits above the black cable connection (see Figure 6). Ignore the top button.

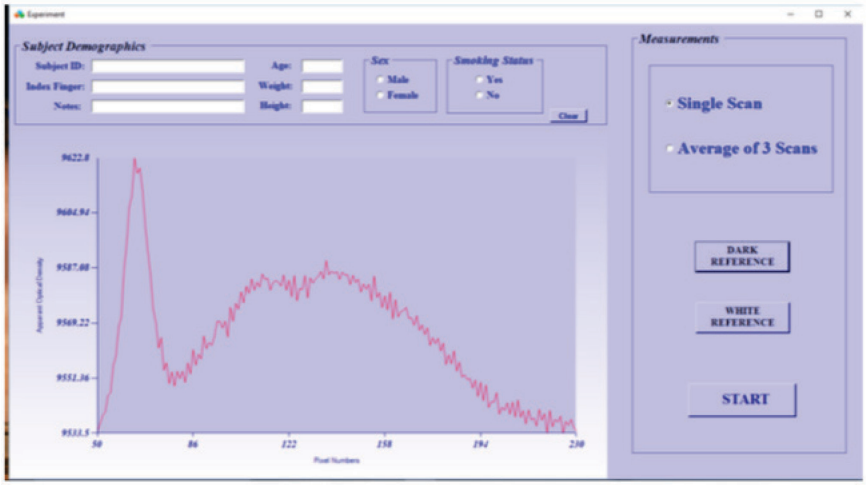
f. The Veggie Meter® takes approximately 5 minutes to warm up. A color display on the top of the housing unit initially displays the number 5 and then counts down the remaining minutes (see Figure 7). After 5 minutes, the display goes dark.

Figure 7. Veggie Meter® Warm-up Display

g. After the display has gone dark, move the computer cursor to the “Longevity_02_25_16 Shortcut” icon on the computer desktop. Double click to activate the program.
h. The Veggie Meter® program window will now open. There are three panels: a) a top panel for entry of subject demographics; b) a right panel for selection of the desired measurement mode (“single scan” or “average of 3 scans”) and for the activation of calibration measurements (DARK REFERENCE and WHITE REFERENCE buttons); and c) a large display panel. The display panel is blank at the beginning.
i. Gently slide the dark reference stick (see Figure 8) with its two side rails over the housing’s finger cradle such that the rails are pointing down and the black felt at the bottom of the stick is facing the lens and positioned a few millimeters above the lens. The stick should push against the two inside plastic pegs while protruding from the housing. While positioned properly, the instrument’s white LED light will illuminate the black felt. Keep felt clean. Do not touch it. Blow off lint/dust if needed.

Figure 8. Veggie Meter® Dark Reference Stick

j. After proper positioning, click on the DARK REFERENCE button located in the right panel of the program window. The display panel will now show the reflection spectrum for the dark reference. It should look similar to the spectrum shown below (Figure 9), consisting of a strong peak at about pix number 70 and a weaker, broad band, in the 80-200 pixel number region. The height/intensity of the strong peak which is indicated on the vertical axis should be ~10,000 $\pm$ 500.

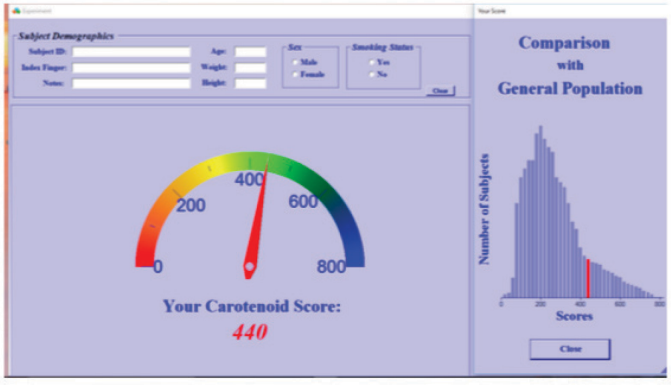


k. Insert the white reference stick into the finger cradle such that the indentation in the white plastic material fits snugly over the contact lens. Make sure the white surface is pointing down.
l. After proper positioning, click on the WHITE REFERENCE button in the right panel of the program window. A spectrum is displayed that should look similar to the one shown above, but smoother, consisting of a strong peak and a broad band. The intensity of the strong peak should be in the range of 42,000 to 56,000.
m. Once calibrated, the instrument is ready for skin measurements.
n. Be sure to calibrate the device after each participant's three readings are completed.

Veggie Meter® Measurement

1. Participant will be asked to wash hands with soap and water prior to measurement.
2. Choose Single Scan mode in the Veggie Meter® display window (we will have participant insert and re-insert finger three separate times, so do NOT choose Average of 3 Scans mode).
3. Enter the participant's ID# into the Subject ID field in the display window. Do NOT enter the participant's name.
4. .
5. Please turn the Veggie Meter computer screen away from the participant to "blind" him/her to the output from the Veggie Meter scan.
6. Ask the participant to insert his/her right index finger. The index finger should be positioned in the cradle such that the finger sits snugly into the indentation (see Figure 10).

7. Click on START. In Single Scan mode, the display window will first flash SCANNING IN PROGRESS, display a progress bar, and after finishing the scan, will show the Carotenoid Score on a scale from 0 to 800 (see Figure 11).
8. In the display panel at the right, the measured score is compared with a histogram of scores for the general population. The histogram region corresponding to the measured score is shown in RED.
9. Record the Veggie Meter® value (i.e., *Your Carotenoid Score*) **BEFORE** clicking the Close button! Record all three of the values on the Tanita print out so the participant can review it after all measurements are completed.
10. Click on the Close button to return to the measurements screen and start a new scan.



11. The measurement data are automatically saved in a folder on disk C called ResultsM. A shortcut is placed on the desktop.

12. Note: The average carotenoid score is approximately 200.

Veggie Meter® Troubleshooting

Sometimes the communication between computer and instrument can be lost. In those cases, corresponding measures will appear in the program window. To re-establish communication, exit the program and/or unplug and reconnect the instrument's USB connections and start over.

Veggie Meter® Shut Down

1. After the scores have been recorded for each participant on the data collection form, turn off the power on the Veggie Meter® housing unit (low button in back).
2. In the measurements screen, click on upper right window button (x) to close program window. In following Exit window, click on the OK button.
3. Pull up main computer menu by sliding up on mouse pad, click on "Power" and "Shut down" on the following window.

Stool Collection Protocol added 3/2/20

Stool Collection and Shipping Instructions Important notes:

1. Please read through all instructions before beginning the collection.

2. Please only collect your sample on Sunday, Monday, or Tuesday.

3. Please select a day when you do not have atypical diarrhea or constipation. We are interested in your usual bowel movement.

4. Please ship your sample, or return your sample to the clinic, within 24 hours of collecting your sample.

5. Please contact [study contact], at [study contact phone number], if you have questions or if you will be returning your sample to the clinic.

Your collection kit contains the following items:

1 Small shipping container with label (paper towels inside)
3 Stool collection tubes with a brown caps
3 Larger clear transport tubes with white caps

3 Biohazard bags

1 Stool collection commode kit

1 Water-soluble bag (clear color)

1 Bubble bag (clear color)
1 Pair of disposable gloves (cream-color)
1 Study questionnaire
1 Blue zip-lock bag

How to collect the stool samples:

STEP 1.

- Lift the toilet seat and place the stool collection frame on the back of the toilet bowl.
- All four corners of the collection frame should be supported by the toilet bowl.

STEP 2.

- Line the collection bowl with the water- soluble bag.

STEP 3.

- Place the toilet seat down.

STEP 4.

- Insert the lined collection bowl into the frame.

STEP 5.

- Place the collection tubes with the brown caps where you can easily reach them— near the toilet or on the back of the toilet.
- After your bowel movement you will use these tubes to collect your stool sample.

STEP 6.

- Sit on the toilet as you normally would. Any stool passed should naturally collect directly into the lined collection bowl.
- Please do not urinate into the collection container. If you do get some urine into the collection container, please select a sample from a part of the stool away from the urine.

STEP 7.

You will collect a total of 3 samples from the same stool: one sample in each of the 3 brown-capped collection tubes.

- Unscrew the brown cap from one tube. There is a scoop attached to the brown cap.
- Please take care not to spill the contents of the tubes because they contain liquid sample preservative and glass beads.
- Please hold the scoop by the brown cap only. Do not touch the scoop.
- While holding the brown cap in your hand, place one full scoop of stool (pea sized) into the small clear tube.
- Screw the brown cap back on tightly.
- Repeat the above steps to collect two additional stool samples in the brown- capped tubes.

STEP 8.

- After collecting your samples, remove the water soluble bag from the collection bowl and place into the toilet.
- The bag will dissolve, allowing you to flush your remaining stool.
- The toilet frame, bowl, and lid can be discarded.

STEP 9.

- Place each brown-capped collection tube into one of the larger white-capped tubes.
- You should have 3 collection sets.
- Screw the caps tightly for shipping.

STEP 10.

- Please vigorously shake the tubes so that the stool mixes well with the sample preservative.

STEP 11.

- Place each of the large tubes inside a biohazard bag and seal the bag completely.

STEP 12.

- Place the 3 sealed biohazard bags with your stool samples into the bubble bag and seal.

STEP 13.

- Please complete the survey on the day of your collection.
- Place the completed survey into the blue ziplock bag

- Place the bubble bag containing the collected samples and the blue ziplock bag containing the survey into the FedEx box.
-

STEP 14.

- Ship the samples within 24 hours of stool collection.

- See next page for shipping instructions.

How to ship your samples:

You may ship your package by FedEx using the instructions below OR you may return your package to the study clinic. Please do not drop off at a FedEx location.

1) Call 1-800-GO-FEDEX (1-800-463-3339) to schedule a home pickup.

2) The automated system will answer and ask what you're calling about. Respond by saying: "Schedule a pick up."

3) Wait to hear all of the options and then press 0.

4) After next options, press 0.

5) Tell the representative: "I would like to schedule a pick-up for express shipment using a prepaid label."

6) The representative will ask you to provide your name, phone number, and address. This information is only for the FedEx pick-up service and will not appear anywhere on your study materials.

7) The representative will ask you two questions, about the number and weight of your packages.
a) The number of packages is one.
b) The weight of the package is less than 5 pounds.

8) The representative will arrange a time for pick-up with you. FedEx can pick-up a package from most locations, including your home or workplace.

If you have any questions about the stool collection procedures, please do not hesitate to contact [field center staff name], at [field center phone number], or email [field center staff email address]

Thank you for your participation in this study!

Stool Receiving Protocol added 3/2/20

1. Receive and sign for samples

2. Find Fedex receipt that matches tracking number and date both copies
    a. One copy will be turned in to Mike, the other kept with the sample
3. Turn on UV light to sterilize biosafety cabinet
4. Open box and remove samples and home survey
5. Verify that the Home Survey ID and sample ID's are the same
6. Remove Fedex packing slip from front of the box
7. Staple the Survey, Fedex Receipt, and packing slip together in that order
8. Add ID, receipt date, sample QC metrics, and time of processing in LIMS
9. Create participant ID labels using brady label maker for cryo tubes
    a. 6 labels for RNALater – Participant ID R
    b. 6 labels for 95% ethanol – Participant ID E9
    c. 6 labels for 100% ethanol – Participant ID E10
10. Label 18 cryo tubes with the labels on the side
11. Clean Biosafety cabinet with ethanol after UV light is off and cabinet blower is on
    a. To cabinet add the following
        i. Biohazard waste bag
        ii. 2 P1000 pipets
        iii. P1000 tips
        iv. Chem wipes
        v. Solvents
        vi. Vortexer if necessary
12. Vortex R sample well for 1 minute or longer if necessary to homogenize sample
    a. Pipet 1mL into first 4 tubes with R label
    b. Add 2mL of additional solvent to wash collection tube
    c. Vortex additional 10-20 seconds
    d. Pipet remaining 2-3mL of sample into last two tubes with R label – DO NOT FILL PAST ¾ MARK‼!
13. Repeat with the two Ethanol tubes using 6 labeled cryo tubes per collection tube
14. Samples to be stored in -80° C in Keyserling Stool Sample boxes. NRI freezers are equipped with temperature notification and back-up generators.
15. Record locations of tubes in Keyserling Sample Sheet (Excel on NRI server) and LIMS
16. Place hard copies (survey, FedEx, packing slip) in locked file cabinet (our floor is key-card access, and the lab door is also locked with restricted access)

8.1.4: Questionnaire data

General protocol for collecting questionnaire data

- See Section 5.5, Strategies for Recruitment and Retention, which outlines how eligibility and baseline questionnaires will be administered.
- In brief, at the outset of the study, participants may decide to complete questionnaires on-line using the REDCap interface or by phone. Whatever method they select for the baseline measures will be maintained throughout the remainder of the study.
- The data collection windows are 4 weeks before baseline, 12 and 24 month follow-up.
- The data collection window is 2 weeks before the 4 month follow-up visit (this is so the participant will have 2 weeks to make changes in behaviors after Counseling Session 4 before completing the questionnaire).

Willett FFQ

- Because of the multiple response options on the Willett FFQ, which would be difficult to read aloud during a phone call, if a participant selects to complete questionnaires by phone, the Willett FFQ will be administered by research staff during the data collection visits (online, using REDCap).
- The recall interval (look-back time frame) for the first administration of the Willett FFQ will be one year (standard look-back for this instrument).
- To capture possible change in dietary intake in response to the intervention, the look back interval for subsequent administrations will be one month.

Medication use

- Our objective is to assess medication use and change in medication use for the following conditions.
    - Diabetes
    - High blood lipids
    - High blood pressure
    - Obesity (FDA approved weight loss medication)
- Within 1 week of a measurement visit, the participant's current medications will be printed for review at the visit.
    - At the visit, the list will be reviewed by the RA and medications associated with the above conditions will confirmed/updated. After the visit, the study medication REDCap form will completed by the RA.
    - If it is apparent that participant is unsure about medications and assistant from a clinician is needed to better determine medication use, Dr. Keyserling will be contacted to call the patient within 2 weeks of the visit to clarify medication use.

Adverse outcomes

- We do not anticipate adverse outcomes to be a consequence of the intervention.
- We will however assess for emergency room visits and hospitalizations at each follow-up questionnaire. If the participant responds positive, then per our HIPAA authorization we will review the EHR to confirm primary reason for emergency room visit and/or admission.
- We will categorize emergency room and hospitalizations as follows:
    - Acute myocardial infarction
    - Angina pectoris
    - Stroke
        - Thrombotic
        - Hemorrhagic
    - TIA
    - Heart failure
    - Coronary bypass surgery
    - Cancer
        - Type of cancer
    - Broken bone
        - Type of fracture
    - Light headedness or dizziness
    - Pneumonia
    - Other infection
        - UTI

        - Other
    - Hypoglycemia
    - Other

8.1.5: Study measures returned to participants

Routine study measures that participants can interpret, will be returned to participants, including:

- Weight
- Height
- BMI
- Blood pressure
- Blood lipids: total cholesterol, HDL cholesterol, triglycerides, LDL cholesterol
- A1c

8.1.6: Study measures available to the participants primary care clinician (PCP)

- The PCP will be notified about high blood pressure as outlined above in Section 8.1.3.2: above.
- The lab report from LabCorp will be uploaded in the EHR. The PCP is made aware of this upload. The lab report includes blood lipids (as above), A1c, and C-reactive protein (CRP)

8.2. SAFETY ASSESSMENTS

As noted, this study is considered minimal risk. That said, the following safety procedures are included as part of this protocol.

- Patients with advanced chronic kidney disease are at increased risk for high blood potassium levels. This risk may be increased by a dietary pattern high in potassium, specifically a pattern with high fruit and vegetable intake, as advocated by our intervention. To reduce this risk, potential participants with advanced renal disease are excluded from this study, as follows:
    - As outlined in Section 5.5, participants screened for the study for whom we can calculate an eGFR based on a previously measured creatinine are excluded if the eGFR < 30 mL/min/1.73 m^2.
    - As outlined in Section 5.4, among participants referred to the study who have not had a creatinine and thus a calculated eGFR as part of their clinical care during the prior 2 years, we will assess creatinine and eGFR as part of the baseline lab work and potential participants will be excluded if eGFR < 30 mL/min/1.73 m^2.
- As part of the physical activity intervention, an information sheet on safety while being active will be given to participants in the intervention group.
- If a participant loses more than 35 pounds at the 4 month follow-up, 80 pounds at 12 month follow-up, or 100 pounds at 24 month follow-up, their study record and the EHR will be reviewed by Dr. Keyserling in conjunction with the participant's PCP to determine if additional evaluation is warranted for underlying medical disease that may be contributing to weight loss.

Addendum 7/25/21 to address high LDL cholesterol (> 190 mg/dL): In addition to uploading LabCorp lab report to Epic with CC copy to PCP (which goes to the Epic in box folder "Media Manager"), will also send Epic staff message to PCP noting LDL >190 if no entry in the chart indicating high LDL already

addressed (most commonly this will be due to statin in tolerance). Rationale for sending "staff message" is that this Epic inbox is likely to be reviewed more frequently than "Media Manager."

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

For this study a serious adverse event includes, as outlined at: *https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html*:

1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. results in inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. 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 (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse)

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

Drs. Keyserling and Berkowitz will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Solicited potential adverse events will occur at each follow-up measurement visit (4, 12, and 24 months). They include the following and we will ask if evaluation for these events included emergency room visit or overnight hospital stay.

- Acute myocardial infarction
- Angina pectoris
- Stroke
    - Thrombotic
    - Hemorrhagic
- TIA
- Heart failure
- Coronary bypass surgery
- Cancer
    - Type of cancer
- Broken bone
    - Type of fracture
- Light headedness or dizziness
- Pneumonia
- Other infection
    - UTI
    - Other
- Hypoglycemia
    - Other

As allowed by our HIPAA authorization, the EHR will be reviewed to confirm the above events and modify the date of occurrence if not accurately provided by the participant. For clinical events that were managed outside of facilities with EHR data available to investigators, we will request that participants sign a release of medical information so that pertinent medical records can be reviewed.

Unsolicited adverse events (AE) or serious adverse events (SAE) may come to the attention of study staff during counseling visits, phone calls, or via other channels of communications. They will be categorized as above and entered into the appropriate follow-up questionnaire at the time of occurrence.

Information to be collected about AEs and SAEs includes event description, time of onset, study clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

Study staff will record events with start dates occurring any time after informed consent is obtained until the last day of study participation.

8.3.5 ADVERSE EVENT REPORTING

Adverse events will be reported as follows:

SAEs that include the following and are 1) definitely, 2) probably, or 3) potentially related to the study will be reported to the chair of the DSMC and IRB within 1 working day:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)

Other SAEs and AEs will be reported to the Chair of the DSMC (by the 15th of each month for the preceding month) and will be summarized for review at each meeting of the DSMC.

Reports of adverse events to the UNC IRB will follow their policy as outlined below:

1. Do not wait to submit a reportable event to the IRB until you have all the information about the event. Report the event promptly and follow-up with additional information as it becomes available.
2. A UPIRSO (Unanticipated Problem Involving Risks to Subjects or Others) that is also a Serious Adverse Event must be reported ASAP, but no later than one (1) week from the time you become aware of the event.
3. All other UPIRSOs must be reported ASAP, but no later than two (2) weeks from the time you become aware of the event.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

As outlined above in Section 8.3.5

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Participants will be aware of events we consider AEs and SAEs as they will be reported to us by participants. Given the low risk nature of this study, we do not anticipate reporting summary information on adverse events to participants. The only "incidental finding" from the lab work reported to patients and PCPs would be an unexpected elevation in CRP. We will instruct the PCP to respond to this type of findings as they would see as appropriate. We do not consider elevations in blood lipids and A1c to be incidental as they likely reflect an underlying biologic process that PCPs are familiar with and able to respond to in an appropriate fashion.

8.38 EVENTS OF SPECIAL INTEREST

N/A.

8.3.9 REPORTING OF PREGNANCY

Pregnancy: Study participants who become pregnant may continue to participate in the study with the understanding that weight loss goals will be suspended during pregnancy through 3 months postpartum. If a pregnant participant wishes to continue with counseling sessions during pregnancy, the focus on counseling will be on dietary quality. The participant may resume full participation 3 months postpartum. Any data collected while the participant is pregnant will be censured and follow-up data will not be collected until the participant is 6 months postpartum.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- 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
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the DSMC. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DSMC ASAP but no later than one week of when the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to DSMC ASAP but not later than within 2 weeks of the investigator becoming aware of the problem

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This randomized trial will compare the effects of a Mediterranean-style (Med-style) dietary pattern intervention to an augmented usual care control group in primary care clinics. The objectives of this trial are:

Primary Aim (efficacy): Weight loss at 24 months. Hypothesis: Mean weight loss in the intervention group will exceed that in augmented usual care by ≥ 4% of initial body weight (e.g., ≥ 5% intervention, ~1% control).

Secondary weight outcomes: Assess difference between study groups in proportion losing ≥ 5% body weight and differences in mean weight loss and proportion losing ≥ 5% across 3 pre-specified subgroups: 1) with vs. without diabetes; 2) females vs. males; and 3) Whites vs. African Americans.

Secondary Aim 1—Physiologic and Lifestyle Outcomes: Assess change in blood pressure, A1c, markers of inflammation, skin carotenoids, and self-reported dietary patterns by study group.

Secondary Aim 2—Process and Psychosocial Factors: Assess process variables (attendance, fidelity, and acceptability of the Med-style dietary intervention), and key behavioral and psychosocial variables, including self-regulation/monitoring skills, self-efficacy, motivation, and quality of life.

Secondary Aim 3--Economic Outcomes: Assess implementation cost, and incremental cost-effectiveness of the intervention relative to control in terms of cost per percentage reduction in weight (i.e., kg lost) and cost per quality adjusted life years (QALYs) gained.

9.2 SAMPLE SIZE DETERMINATION

Note: the text below was written for an anticipated sample size of 350. We now plan to enroll 360 participants.

For our primary outcome, percent change in weight at 24 months, we have calculated sample size based on a two-sided test of significance with α=0.05 and the standard deviation (SD) of percent change in weight of 7.3% as observed in the Heart Health Lenoir Project[74, 75]. Table 4 illustrates sample size calculations (allowing for 20% attrition) for various differences in mean changes between study groups based on a 1:1 randomization allocation ratio. This table also provides power calculations to detect differences in weight change compared to control separately for pre-specified subgroups (those with vs. without diabetes, female vs. male, and white vs. African American assuming no sub-group is less than 40% of the overall sample). We expect the intervention to reduce weight by at least 5% and that average weight loss in the intervention group will exceed that in augmented usual care by at least 4% (we estimate weight loss in usual care of ≤ 1%). Our plan to enroll 350 participants provides excellent power for our primary outcome (>99%) and reasonable power (82%) within each of our pre-specified sub-groups. For a difference between groups as small as 3%, we still have robust power for our primary outcome. Although we do not anticipate major differences in weight loss between those in our pre-specified subgroups, we will test the potential for large differential effects between subgroups using interaction terms. However, under the assumptions described above, our power to detect realistic difference in effects of 2-3% between these subgroups will be limited (about 20-40%). Also, for a difference in proportions of those losing ≥ 5% body weight as small as 15% (e.g., 15% control vs. 30% intervention), allowing for attrition, the proposed sample size provides 85% power. For several secondary outcomes, we present in Table 5 minimally detectable differences corresponding to effect size of 0.33 for the sample size of 360 with 20% attrition, 80% power, and α =0.05

Table 4. Power Estimates for % Change in Weight at 24 Month Follow-up

Assumed Mean % Change Difference Between Groups	Total Sample Size	Overall Power to Detect Difference	Minimum Power within Each Subpopulation (Diabetes status, sex, and race) to Detect Specified Difference
3	300	89%	51%
	350	93%	58%
	400	96%	64%
4	300	98.8%	76%
	350	99.5%	82%
	400	99.8%	87%

Table 5. Secondary Outcomes (at 24 month)

Secondary Outcomes	SD of change	Difference in mean changes
Systolic BP	23.1	7.6
Diastolic BP	11.1	3.6
A1c (%)	0.4	0.1
CRP	0.9	0.3
Dietary pattern assessed by	0.3	0.1

9.3 POPULATIONS FOR ANALYSES

Intention-to-Treat (ITT) Analysis Population (i.e., all randomized participants)

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

This is covered in Section 9.4.2.

Update 6/8/25: Our analysis plan as submitted with this protocol is below. Before we assessed study outcomes, we prepared a more detailed statistical analysis plan. This is include in 9.4.3 below:

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary analysis will be conducted using the ITT Population and will be repeated secondarily using the Per Protocol Population.
Percent change in body weight = (Follow-up weight – baseline weight)/baseline weight x 100.
We will compare the longitudinal mean % change in body weight between groups using analysis of covariance (ANCOVA), conducted using a linear mixed model. A mixed model will allow for the inclusion of all observed follow-up data for all participants. The model will include fixed effects for group, follow-up visit (4, 12, or 24 months), group-by-visit interactions, site, baseline weight, race/ethnicity, sex, and diabetes status. To account for within-participant correlation, the model will allow for correlated error terms using an unstructured covariance matrix. For the primary comparison, we will use an appropriately specified linear contrast of the model parameters to test for a treatment effect at 24-months at the 5% significance level. Secondarily, we will compare the groups at other time points and will estimate effect sizes along with 95% confidence intervals for each comparison. Secondarily, we will expand the model by including appropriate interaction terms, one at a time, to examine the potential heterogeneity of intervention effect in sub-groups, including diagnosis (diabetes vs. no diabetes), race/ethnicity, sex, and by degree of baseline obesity (BMI > 40 vs. less). Interaction terms will be tested at the 5% significance level.
We will use a longitudinal mixed effects logistic regression model to compare the groups for proportions losing > 5% body weight at each follow-up visit; estimates of odds ratios and 95% confidence intervals will be provided. This model will control for the same covariates specified for the primary model.
Missing Data
We will make every effort to prevent missing data and to minimize attrition, however some dropout is expected. We will record reasons for dropouts to formulate realistic assumptions about observations that are missing, and compare respondents and non-respondents for differences on values of non-missing variables. We will conduct a series of sensitivity analyses using similar models to evaluate the robustness of conclusions drawn from the primary model to departures from MAR assumption by comparing the magnitude of the primary treatment contrast. Specifically, we will use 1) multiple imputation including auxiliary information about the missingness; 2) shared-parameter models for not missing at random analyses where one variable is the efficacy outcome and the second variable is time to dropout, linked by a set of latent variables that are assumed to influence both the outcome and the

time to dropout; (3) patterning-mixture model, with models for each pattern of missing ness (e.g., by study phase); and (4) worst-case imputation, with baseline carried forward for intervention participants and best observation carried forward for control participants**.**

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Analysis of Secondary Objectives (1-2)

The ITT Population will be used in the primary analysis of all secondary outcomes. Similar ANCOVA methods to those described above will be used to compare groups on each of the secondary outcomes; for any outcome measured at baseline, the corresponding ANCOVA will control for baseline value in addition to the covariates noted above. Blood pressure will be averaged over three repeated measurements at each visit. Because they are of secondary interest, tests on secondary outcomes will each be conducted at the 5% significance level with no adjustments for multiple comparisons. All estimates of effect size will be accompanied by 95% confidence intervals. Data from all secondary outcomes will be presented regardless of extent of "significance".
Descriptive summaries of process data (attendance at intervention contacts, fidelity to intervention delivery, and acceptability of the Med-style dietary pattern) will be provided for participants randomized to Group 1 in the ITT Population. No inferential statistics (p-values or confidence intervals) will be presented.

Analysis of Secondary Objective 3 (Economic Analysis)

We plan to conduct both a budgetary impact assessment and a cost-effectiveness analysis. The budgetary impact assessment will quantify the total and per participant costs of intervention delivery from the health system perspective using an Activity Based Costing (ABC) approach and cost tracking forms that the health economist (Finkelstein)[158-160] has developed and refined in past behavioral trials. Using this approach, all relevant labor, materials and supplies, contracted services, and other relevant costs required to deliver the interventions will be captured by key activities. This information will allow policy makers to identify the total and per capita fixed and variable costs of the intervention and to forecast required budgets, should the intervention expand beyond the trial phase. The non-sunk cost estimates will also feed into the cost-effectiveness analysis.

The incremental cost-effectiveness analysis will follow the approach Dr. Finkelstein has employed in prior studies, including a manuscript on the cost-effectiveness of commercial weight loss programs.[161, 162] We will compute the incremental cost per kilogram of weight loss relative to control, and using the approach presented in Finkelstein and Kruger,[161] the incremental cost per quality adjusted life year (QALY) gained. The numerator for this analysis will be the incremental program delivery costs of the intervention relative to control, minus any cost offsets based on differences in health services and medication use across arms. The denominator will be the incremental QALYs based on average differences in EQ5D[146] scores across arms collected at each assessment point. These scores can be used to quantify net QALY differences during the intervention period. In the base case, we will assume that QALY benefits decay linearly to 0 by the end of the second year post cessation of the study. All out-year cost and QALY estimates will be discounted at 3.5% per annum.

To test for the sensitivity of our incremental cost-effectiveness ratio (ICER) estimates to changes in key inputs, we will conduct one-way sensitivity analyses by (1) doubling or halving all key model inputs; and

(2) varying the duration of benefit decay post program cessation from 2 years in both base cases to 0, 1, and 3 years. We will also conduct probabilistic sensitivity analyses to assess the effect of uncertainty regarding all input parameters using appropriate distributions for all cost and QALY values. Using the results, we will produce cost-effectiveness acceptability curves that graphically present the probability that the intervention is cost-effective for a range of willingness to pay metrics that a decision maker may consider. Based on the results, we will discuss the extent to which the intervention is likely to be both affordable and cost-effective

6/9/25: Note: a separate Statistical Analysis Plan was prepared for this study. This will be submitted to clinicaltrials. gov and journals as a separate document.

9.4.4 SAFETY ANALYSES

Prior to analysis, any data-captured adverse events will be coded by the principal investigators. Each type of event (by seriousness, severity, relationship to study) will be descriptively summarized in frequency tables by group (including only a single occurrence of any distinct type of event for any participant). Number of CVD events, ER visits, and hospitalizations will also be descriptively summarized by group. No inferential statistics (p-values or confidence intervals) are planned for comparing safety data between groups.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

We will summarize baseline data (i.e., pre-randomization data) for the ITT Population. Measures of central tendency and dispersion for continuous and certain discrete variables will include means, standard deviations, medians, minima, and maxima. Categorical data will be summarized with frequencies and percentages. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables. No inferential statistics (i.e., p-values and/or confidence intervals) for comparing data between groups will be presented.

9.4.6 PLANNED INTERIM ANALYSES

N/A.

9.4.7 SUB-GROUP ANALYSES

Our pre-specified sub-groups are diabetes, race, and sex.

Our plan to enroll 360 participants provides excellent power for our primary outcome (>99%) and reasonable power (82%) within each of our pre-specified sub-groups. For a difference between groups as small as 3%, we still have robust power for our primary outcome. Although we do not anticipate major differences in weight loss between those in our pre-specified subgroups, we will test the potential for large differential effects between subgroups using interaction terms. However, under the assumptions described above, our power to detect realistic difference in effects of 2-3% between these subgroups will be limited (about 20-40%). Also, for a difference in proportions of those losing ≥ 5% body weight as small as 15% (e.g., 15% control vs. 30% intervention), allowing for attrition, the proposed

sample size provides 85% power. For several secondary outcomes, we present in Table 5 minimally detectable differences corresponding to effect size of 0.33 for the sample size of 360 with 20% attrition, 80% power, and α=0.05

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A.

9.4.9 EXPLORATORY ANALYSES

N/A.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATION

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are submitted with this protocol:

- Consent form
- Consent form for stored specimens
- HIPAA authorization
- Note: these forms will be updated per modifications approved by the IRB

Consent form dated 9/23/19

University of North Carolina at Chapel Hill
Consent to Participate in a Research Study
Adult Participants

Consent Form Version Date: March 2, 2019
IRB Study # 19-1712
Title of Study: Randomized Explanatory Trial of a Mediterranean Dietary Pattern Weight Loss Intervention for Primary Care Practice—also known as the DELISH (Delicious Eating for Life in

Southern Homes) Study
Principal Investigator: Thomas Keyserling, MD, MPH
Principal Investigator Department: Medicine-Internal Medicine
Principal Investigator Phone number: (919) 445-6794
Principal Investigator Email Address: thomas_keyserling@med.unc.edu
Funding Source and/or Sponsor: NIH National Heart, Lung, and Blood Institute (NHLBI)

Study Contact Telephone Number: 919-843-9563
Study Contact Email: kiira_lyons@med.unc.edu

SUMMARY
Intensive weight loss programs (14 or more counseling sessions over 6 months) are recommended for patients with a body mass index (BMI) greater than 30, yet long-term weight loss is often modest and many prior weight loss programs have not focused on what we now know to be a healthy eating pattern. This study will compare a new weight loss program that focuses on a healthy eating pattern (call Med-South) with WW™ (formally Weight Watchers™), an effective and widely available weight loss program. Those who take part will be randomly assigned (like flipping a coin) to either the new weight loss program or WW™. Both programs will last for 2 years with measurement visits at the start of the study and at 4, 12, and 24 month follow-up.

This is a low-risk study, as both weight loss programs follow current guidelines for such programs. There may be minor pain from the blood draws at each measurement visit. Intensive weight loss programs do involve many counseling visits so taking part does require a time commitment, as described below. We expect participants in both study groups will lose weight and consider this a benefit of taking part in the study.

Introduction:

We invite you to take part in this research project. This form tells you about the project so you can decide if you want to join this study. If you do, you can change your mind and withdraw at any time. We think you will benefit from taking part in this study, but you may not, as the purpose of research studies is to gain new knowledge that may help others in the future. There also may be risks to being in a research project and these are noted on this form. If you do not take part in this study or you start the study and then decide to stop taking part before it is done, your decision will not be a problem for your doctors or other health care providers.

What is the purpose of this study?

The purpose is to develop and test a new weight loss program that includes a major focus on a healthy dietary pattern. A healthy dietary pattern includes eating more foods with high-quality fats (vegetable oils, nuts, seeds, fish) and high-quality carbohydrates (fruits, non-starchy vegetables, whole grains, and beans) and eating fewer foods with poor quality carbohydrates (sugar sweetened beverages, refined grains, and many processed foods). The eating pattern we are testing is similar to a Mediterranean dietary pattern. We call this new weight loss program

the “Med-South Weight Loss Program” because it will be tested in the southern US. To learn if the Med-South Weight Loss Program is more effective than currently available weight loss programs, we will compare it to WW™ (formally Weight Watchers™). We have selected WW™ because it is an effective weight loss program that is widely available.

You are being asked to be in this study because your Body Mass Index (BMI) was greater than 30 (when last checked at the clinic) and your doctor approved for you to take part because he or she thinks you might benefit from losing weight.

How many people will take part in this study?
There will be about 360 people in this research study.

How long will your part in this study last?
About 2 years.

What will happen if you take part in the study?
Frist, we mailed you the study brochure and then study staff called to confirm that you are eligible and to see if you want to take part. If so, we mailed or emailed you this consent form. Next, we will call to answer any questions about this form. After doing so, if you want to take part, we will give you instructions on how to sign this form electronically or you may sign it at your first study visit. Then, we will discuss how to complete the study surveys before the first visit.

You may fill out these surveys online or over the phone (study staff will call and ask you the questions). If you decide to complete them over the phone, we will mail you one survey to complete before you come in (the survey goes over what you eat). If you do not want to complete this in advance, just bring it to the first visit and we will complete the form then. We expect it to take about 1.5 hours to fill out all surveys that ask about your lifestyle behaviors (like eating and physical activity habits) and other questions about your health. **(You do not need to** complete them at one time.) Once you’ve filled out the surveys, we will set up a time and date for your in-person enrollment visit.

The enrollment visit, follow-up measurement visits, and in-person counseling visits will take place at the UNC Center for Health Promotion and Disease Prevention, 1700 Martin Luther King, Jr, Blvd., Chapel Hill, NC, which is located about 5 miles north of the UNC main campus. (We will send instructions on how to get to our office.) We will ask you to fast for 9 hours and avoid caffeine for 30 minutes before the enrollment visit and the other measurement visits. We will schedule these visits in the morning unless you ask for a visit later in the day. If you have not already signed the consent forms on line, we will start the first visit by having you sign the consent forms. Then, we will check to see if all surveys have been filled out and complete any that may not have been done. Next, we will review your current medication listed in the UNC medical record and record medications you are taking for diabetes, high blood pressure, high cholesterol, and for heart burn or stomach ulcers. Before moving on to the measures outlined below, we will invite you to empty your bladder (recommended before measuring blood pressure).

Next, we will ask you to put your finger in an instrument that checks skin carotenoid levels (which tell us about how much fruit and vegetables you eat or drink). This test does not hurt and takes less than 3 minutes. We will also check your weight, height, and blood pressure. After that, we will collect a blood specimen (about 2 tablespoons). We will measure total cholesterol, HDL cholesterol, triglycerides, and A1c (a test of your blood glucose over the past 3 months). We will report the results of these test to you and your primary care clinician. We will also do some special research blood tests to look at how what you eat impacts blood inflammatory markers. If you agree, we will also store blood for future research.

There is a great deal of scientific interest in how dietary patterns may change the bacteria that live in your intestines (the microbiome) and if these changes impact weight change. So that we can learn if your microbiome changes in response to the weight loss programs, we invite participants to submit stool samples. This part of the study is voluntary. If you agree to do so, we ask you to collect and return (by mail) a stool sample within 2 weeks of the enrollment visit. For follow-up measurement visits, we may send you the collection kit in advance of the visit. Study staff will go over the instructions for collecting these samples at your first visit.

It will take about 30-45 minutes to complete the measures outlined above and to collect your blood sample.

After we collect the blood sample, study staff will randomly assign you (like flipping a coin) to receive either the Med-South Weight Loss Program or WW™. If you are assigned to the Med-South Weight Loss Program, you will receive your first counseling session, which should take 45-60 minutes. If assigned to WW™, we will give you instructions on how to get started with this program, which should take about 15-30 minutes. If you bring your smart phone to the visit, we will help you download the WW™ App. Also, whichever group you are in, you will be encouraged to do moderate physical activity, like brisk walking, which is recommended for all Americans.

Please note, WW™ is a safe and effective program that is considered a standard for community-based weight loss programs. If you are randomized to this program, we encourage you to engage with the program and take full advantage of what it has to offer. We do not know if the new program we have developed is better than WW™. That is what we hope to learn in this study. If it turns out the Med-South Program is better, then components of the Med-South Program may be added to other weight loss programs in the future.

Med-South Weight Loss Program
Most weight loss programs offer weekly one-on-one or group counseling sessions for 16-20 weeks. The Med-South Weight Loss Program is different and is given in 3 phases. The program begins with **Phase I**, a 4 month lifestyle phase that focuses on the "basics" of healthy eating rather than weight loss. Over the next 8 months in **Phase II**, we focus on weight loss, followed by a year-long (**Phase III**) phase to help you maintain weight loss. In Phases I, the main counseling sessions are given monthly, followed by check-in phone calls 1-2 weeks later. In Phase II, the main counseling sessions will occur weekly for 6-8 weeks, depending on your progress. There are also check-in phone calls--the number will vary based on your progress.

During Phase III, there are 2 main visits and follow-up phone calls. More details about these visits are in the table below.

Some of your counseling visits will be face-to-face with your counselor and some by phone. Only one member of a family may join this study, but other family members are invited to take part in face-to-face and phone counseling sessions. The face-to-face format will be required for a total of 5 visits – the *first visit* in each of the 3 phases (right after study measurements at enrollment and 4 and 12 months), 2 months after starting the weight loss program in Phase II, and mid-way during Phase III (about 18 months after starting the Program). The other sessions may be done by phone or in-person. During Phases II and III, when you come to our office for a face-to-face counseling session, we will also check your weight.

During face-to-face sessions, you and the counselor will sit side-by-side and use a web-based program or the paper format to review educational materials, select dietary goals, and list first steps to reach these goals. If the phone format is used for major counseling sessions, you may view the educational content online or use your paper version. The program also includes brief telephone calls to check on progress towards goals selected at previous sessions and provide support for lifestyle change. The number of phone calls you get will depend on if you are meeting your personal weight loss goals in Phase II or keeping the weight off in Phase III. The table below has more information.

Phases	**# Contacts**	**Contact Length**	**Estimated Total Contact Time**

Phase I	• 8 total
	  ○ 4 core sessions: the first must be in-person; choice of in-person or phone for all others
	  ○ 4 follow-up phone calls
		• Core session = 45-60 min.
		• Follow-up call = 15 min.
			4 - 5 hours

Phase II	• 14 core sessions: the first and a visit about 2 months later must be in-person; choice of in-person or phone for all others. • 6-12 follow-up phone calls	• Core session (in-person) = 45-60 min. • Core session (phone) = 30-45 min. • Follow-up call = 20-30 min.	8.7 – 14 hours (core) 4.7 – 9.5 hours (Follow-up)
Phase III	• 2 core sessions (both in-person) • 12-24 follow-up phone calls (1-2 per month)	• Core session (in-person) = 45-60 min. • Follow-up call = 15-20 min.	1.25 – 2 hours (Core) 3 – 8 hours (Follow-up)
2-Year Program TOTAL	**44 – 60 Contacts**	**--**	**21.7 – 38.5 hours**

If you agree, we may audio-record a few counseling sessions for quality improvement purposes (to check on how our counselors are doing and provide feedback on areas needing

improvement). These recorded sessions will be kept as electronic files but without information that could be used to identify you (other than your voice).

WW™ Weight Loss Program

If you are randomized to WW™, you will have access to both the workshop and digital components of the WW™ Program for 2 years. WW offers in-person coaching and community-based learning through weekly Workshops at WW™ Studios. The Workshop component allows for attending weekly group meeting at a WW™ studio (local WW™ office).

The Digital component can be accessed using the WW™ website or a smart phone App. The digital tools available in the WW™ Digital program include food tracking (either manually or with bar code scanning), progress charts, lifestyle coaching with 24/7 chat with a WW Coach, ability to track activity (manually or by syncing a fitness tracking device), incentives for behavior change (WellnessWins), recipes, and even local restaurant recommendations using GPS. You will also have access to Connect, a digital community for WW™ members. Study staff will provide basic instructions on how to use the WW™ digital resources.

The WW™ Program uses "SmartPoints" assigned to foods based on energy content and nutritional value, allocating a certain number of points to users daily based on their starting weight, weight loss goals, age, and sex. You'll receive a personalized SmartPoints budget made up of Daily SmartPoints, plus some extra Weekly SmartPoints for those days when you need a "cushion."

It you are assigned to the WW™ Program, you get to decide how many workshops to attend and how often to use the digital program. You can decide to not attend the workshops and only use the phone App and/or website.

Follow-up measurement visits
About 4, 12, and 24 months after starting the study, we will ask you to return for follow-up measures, which will be like those collected at study enrollment. We will ask you to fill out surveys online or by phone before this visit. It will take about 1 to 1.5 hours to fill out the surveys and 30 minutes for the measurement visits. Please note that for us to understand if the Med-South Weight Loss Program is effective, we have to carefully measure many study outcomes. Most of these outcomes are measured by questionnaire. The amount of blood work drawn for measurement is similar to that taken at routine office visits when several tests are ordered (about 2 tablespoons at baseline and 12 months; and 1.5 tablespoons at 4 and 24 months). The stool test is optional. As outlined below, we will compensate for your time spent on measurement at a rate of $20 to $30 dollars per hour. And we thank you in advance for your willingness to complete this very important part of the study.

Will I be informed about the study's findings?
We will inform all who take part about the study's findings. If the Med-South Weight Loss Program results in greater weight loss, we will make the Med-South Program materials available to those who received the WW™ Program.

Should I take part in this study?
Prior research indicates that for weight loss studies to be effective, they must offer an intensive intervention, defined as at least 14 sessions over a 6-month period. That is why the Med-South Program includes many contacts and why WW™ suggests frequent contact with their program. So, you need to ask yourself if you are willing to make this type of commitment to a weight loss program. If you are, we welcome you to this study! We will do all we can to accommodate your schedule or any special needs you may have as you take part in the weight loss programs and return for measurement visits.

What are the possible benefits from being in this study?
We think you may benefit from being in this study by improving your lifestyle and losing weight. However, you may not benefit from being in this study.

What are the possible risks or discomforts involved from being in this study?
The possible risks and discomforts from being in this study are few and are listed below.

- We do not think there is risk to you from the dietary advice given as part of the Med-South Program or WW™.
- Eating less is a part of standard weight loss programs. If you do not eat enough, you could lose weight too fast. By asking you to check your weight often, the weight loss programs in this study will let you know if and when you are losing weight too fast.
- Although doing more physical activity is not the main focus, both weight loss programs will recommend you do moderate physical activity. Those who increase their level of physical activity may experience minor muscle pain (this is common, affecting more than 50 in a 100 people), but this type of activity rarely (fewer than 1 in a 100) causes serious health problems such as chest pain or asthma.
- For those with diabetes, losing weight and reducing carbohydrate in the diet can lead to lower blood sugar, including hypoglycemia. This has occurred in less than 1 in a 100 people in our past studies. We will provide those with diabetes information on how to reduce the risk of low blood sugar.
- For those with high blood pressure, losing weight can lead to lower blood pressure, which can cause dizziness and even falls. Adverse outcomes related to low blood pressure are very rare in weight loss studies, occurring in less than 1 in a 100 people. Typically, the blood pressure is lowered slowly with weight loss, allowing your doctor time to observe the lower blood pressure and reduce your blood pressure medicine.
- A blood sample will be collected by trained staff. The risk of minor pain is very common (in more than half of people). Bruising does not happen often (about 1-10 of every 100 persons) and the risk of infection or fainting is rare (fewer than 1 in 100).
- In all studies, there is a very slight chance of loss of privacy (that is, others may see your study information). As stated below, we will do all we can to make sure this does not happen.

Also, there may be other risks we did not list here. You should report to the research team any problems that may be due to this study.

What if we learn about new findings or information during the study?
You will be given any new information gained during the study that might affect the risk of taking part in this study.

How will information about you be protected?
Your study bloodwork for routine tests (cholesterol levels and A1c) will be stored with your name as this will be sent to a commercial lab for analysis (LabCorp). These samples are typically thrown away 3 days after collection. Your study surveys and bloodwork for the inflammatory markers will be stored with your study ID number and your first and last initial, but NOT with your name (we call this de-identified data). No one other than study staff will be able to connect your name and study ID as we will follow standard procedures to protect the privacy of research data.

We may use your de-identified data, as described above, in future research without additional consent. However, in some cases, the Institutional Review Board (called IRB and described below) may require that you be re-contacted and asked for your consent to use your data in a specific research study. You have the right, at that future time, not to participate in any research study for which your consent is sought.

Participants will not be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by agents of the University or research sponsors for purposes such as quality control or safety.

By signing this informed consent document, you agree that some of the information generated by participating in this study and/or a copy of the consent form may be included in your medical record and that this information may be viewed by other physicians or caregivers who provide healthcare services to you. This will allow the doctors caring for you to know what tests you may be receiving as a part of the study and know how to take care of you if you have other health problems or needs during the study.

What is a Certificate of Confidentiality?
This research is covered by a Certificate of Confidentiality. With this Certificate, the researchers may not disclose or use information, documents or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings in the United States, for example, if there is a court subpoena, unless you have consented for this use. The Certificate cannot be used to refuse a request for information from personnel of a federal or state agency that is sponsoring the study for auditing or evaluation purposes.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law, such as mandatory reporting requirements for child abuse or neglect, disabled adult abuse or neglect, communicable diseases, injuries caused by suspected criminal violence,

cancer diagnosis or benign brain or central nervous system tumors or other mandatory reporting requirement under applicable law. The Certificate of Confidentiality will not be used if disclosure is for other scientific research, as allowed by federal regulations protecting research subjects or for any purpose you have consented to in this informed consent document.

What will happen if you are injured by this research?

It is not likely that you will be injured by this research, but all research involves a chance of injury. If a medical problem occurs, the researchers will help you get medical care, but costs for this care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for injuries or medical care. However, by signing this form, you do not give up any of your legal rights.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. The research team also has the right to stop your participation at any time. This could be because you have had an unexpected reaction, or did not follow instructions, or because the entire study has been stopped.

Will you receive anything for being in this study and will it cost you anything to take part?

You will receive the weight loss program and lab work free of charge. You will receive $60 payment for your time devoted to study measures at the start of the study and at 4, 12, and 24 month follow-up. The payment rate is $20-30/hour. If you complete all measurement visits, you will receive a total of $240. In addition, you will receive $30 reimbursement for each stool specimen you submit.

We will calculate the one-way distance from your home address to our research office and will reimburse mileage for measurement visits as below. Note, there is *no reimbursement for mileage* if you attend a WW™ workshop or if you come in for a Med-South Weight Loss Program counseling visit that does not include a measurement visit (measurement visits are: enrollment visit and 4, 12, and 24 month follow-up visits). Parking is free. All reimbursement will be by gift card.

Mileage reimbursement rate:

- Less than 10: $0
- 10-19 miles: $10
- 20-29 miles: $20
- 30-39 miles $30
- 40-49 miles $40
- 50-59 miles $50
- 60 or more $60

Who is sponsoring this study?
This study is funded by the National Heart, Lung, and Blood Institute (NHLBI). This means the research team is being paid by NHLBI for doing the study. The researchers do not have a financial interest in the final results of the study.

What if you are a UNC employee?
Taking part in this research is not a part of your University duties and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What if you have questions about your rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Participant's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

I also agree to submit stool samples as part of my participation in this study.

____ yes

_____no

_____ _____
Signature of Research Participant Date

_____
Printed Name of Research Participant

_____ _____

Signature of Research Team Member Obtaining Consent Date

_____

Printed Name of Research Team Member Obtaining Consent

University of North Carolina at Chapel Hill
Consent for Storing Biological Specimens <u>With</u> Identifying Information

Consent Form Version Date: 3-2-2020
IRB Study # 19-1712
Title of Study: Randomized Explanatory Trial of a Mediterranean Dietary Pattern Weight Loss Intervention for Primary Care Practice—also known as the DELISH (Delicious Eating for Life in Southern Homes) Study
Principal Investigators: Thomas Keyserling, MD, MPH
Principal Investigator Department: Medicine-Internal Medicine
Principal Investigator Phone number: (919) 445-6794
Principal Investigator Email Address: thomas_keyserling@med.unc.edu
Funding Source and/or Sponsor: NIH National Heart, Lung, and Blood Institute (NHLBI)

Study Contact Telephone Number: 919-843-9563
Study Contact Email: kiira_lyons@med.unc.edu

CONCISE SUMMARY

See study consent form for summary of the overall study. This form provides information about stored specimens that may be collected as part of this study. Providing stored specimens for the study is optional. As outlined in the study consent form, blood samples will be obtained at enrollment and at 4, 12, and 24 month follow-up. If you agree to allow the researcher to store your blood specimens for future research, an additional tube of blood (about 2 teaspoons) will be collected at the enrollment visit and 12 month follow-up visit. Research using your stored

specimens may help the researchers better understand how your body responded to the weight loss interventions. This research will also allow us to understand if your response to the intervention is related to your genes.

The following information about research related to use of stored specimens is covered in study consent form:

- **What are some general things you should know about research?**
- **How will information about you be protected?**
- **What is a Certificate of Confidentiality?**
- **What will happen if you are injured by this research?**
- **Who is sponsoring this research?**
- **What if you have questions about this research?**
- **What if you have questions about your rights as a research subject?**

What is the purpose of this specimen repository or "biobank?"

Research with blood, tissue or body fluids (specimens) can help researchers understand how the human body works and help answer research questions about how the body responds to different weight loss programs. It is possible that this type of research my help researchers improve weight loss interventions and even develop new products, such as drugs. This type of research includes genetic research. Sometimes researchers collect and store many specimens together and use them for different kinds of research, or share them with other scientists; this is called a specimen repository or "biobank."

The purpose of this particular repository or biobank is to have specimens that may be used to better understand weight loss interventions. Future research done with these specimens may include genetics research. Information on genetics research, including risks, is provided in the next section.

Information on genetics research and risks of this research

As genes are so important to our health, it is very common now for research studies to include genetic tests as we may do with stored specimens collected for this study. If done, the major focus of the genetics research would be to see if genes or groups of genes help us to better understand how you responded to the weight loss programs. If you give a blood sample for genetics research, it will become the property of the UNC Chapel Hill and the sample may be kept for years. If you decide you want to withdraw from the genetics part of this study, contact the researcher listed above. The primary risk of genetic research is loss of privacy and as noted on this form, we will take all routine steps to reduce this risk. That said, it is important for you to be aware of the following:

- A Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.
- The National Institutes of Health (NIH) has established a national database that will hold information from many individuals across the country, including medical information and genetic information. If information about you is sent to this national database, it will not be identified (that is, no one can tell whose information it is). This information may include sequencing your entire genome (all of your genes). Also, access to this information will be controlled and limited to other researchers.

Will you receive results from the genetics research?
Most genetics research is not expected to yield new information that would be meaningful to share with you personally. There are no plans to re-contact you or other participants with information about research results. The use of your samples may result in commercial profit. You will not be compensated for the use of your samples.

In a few participants, however, we may find genetic variants that are not related to the purpose of this study, but that are related to other medical conditions. These variants are rare and we expect to find them in fewer than 5% of the people who take part in this study.

- If you have one of these variants, it suggests that you have a serious medical condition that can be treated OR that you have a high risk for a future medical problem that can likely either be prevented or more successfully treated if doctors know about it ahead of time.
- An example of one of these conditions is hereditary cancer predisposition. If you have a condition like this, your doctor may recommend special screening to look for early cancers that would be more easily treated, or in some cases preventive surgery to reduce the risk of developing cancer.
- If you have one of these variants, your children would be at risk to have inherited it from you. In addition, it may have been inherited from one of your parents, and others in the family (siblings, aunts/uncles, cousins etc.) might also be at risk to have the variant.
- In the event that your genetic analysis suggests you have one of these variants, we will ask you for a separate sample using a saliva kit so that the finding can be confirmed by the clinical laboratory and reported to you by a clinical Genetic Counselor. The results will be included on a clinical laboratory report and it will become part of your UNC medical record.
- The genetics team may make health care recommendations for you and your family based upon the genomic sequencing results. These recommendations might include other clinic visits and evaluations for you and other relatives. These evaluations can provide important information about their need for medical care. These other visits, tests, and evaluations are not part of this study and will not be paid for by the study.
- The American College of Medical Genetics and Genomics recommends that, when genomic sequencing is done, these variants should be looked for, interpreted, and reported.

How will the specimens be collected?
At the baseline visit and at the 1 year visit, 10 ml (2 teaspoons) of blood will be collected. This will be done during the same blood draw as other study tests so this will NOT involve another needle stick. The specimen will be labelled with a study number only.

What will happen to the specimens?
The specimens will stored in a freezer on the campus of UNC-Chapel Hill. The code linking the number of on the specimen to your identifying information will be stored on a password protected computer. Only study researchers will have access to the code linking the study number of the tube to your identifying information.

What are the possible benefits to you?
Benefits to you are unlikely. However, as outlined above, if genetic variants are found that suggest you have a serious medical condition that can be treated OR that you have a high risk for a future medical problem that can likely either be prevented or more successfully treated if doctors know about it ahead of time, we will contact you with this information. This information may be beneficial to your health.

What are the possible risks or discomforts involved with the use of your specimens?
As the blood will be drawn at the same time as the routine study blood (during the same "stick") there are not additional risks associated with collecting this specimen.

There is a risk of breach of confidentiality. If this research involves genetics, there is also a potential risk for some of your relatives and other members of your ethnic group, since they share some of your genetic makeup.

Will researchers seek approval from you to do future studies involving the specimens?
By signing this consent form, you are giving your permission for researchers to use your specimens as described above. Current and future research is overseen by a committee called the Institutional Review Board (IRB). The role of the IRB is to protect the rights and welfare of research participants. We may use de-identified data and/or specimens from this study in future research without additional consent. However, in some cases, the IRB may require that you be re-contacted and asked for your consent to use your specimens in a specific research study. You have the right, at that future time, not to participate in any research study for which your consent is sought. Refusal to participate will not affect your medical care or result in loss of benefits to which you are entitled.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from having your specimen collected. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. However, by signing this form, you do not give up any of your legal rights.

Will you receive results from research involving your specimens?
Most research with your specimens is not expected to yield new information that would be meaningful to share with you personally. There are no plans to re-contact you or other subjects with information about research results, except as outlined above.

Can you withdraw the specimens from the research repository?
If you decide that you no longer wish for the specimens to be stored, you should contact the researchers on the front page of this form. It is best to make your request in writing.

Any analysis in progress at the time of your request or already performed prior to your request

being received by the researcher will continue to be used as part of the research study. Once the researchers have been notified, your remaining specimens would be destroyed. If you do not make such a request, the specimens may be stored forever. The researchers may choose to destroy the specimens at any time.

Will there be any cost to you for storage of the specimens?
There will be no cost to you for the storage and use of the specimens for research purposes.

What if you have questions about your rights as a research subject?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously if you wish, the Institutional Review Board at 919-966-3113 or by e-mail to IRB_ subjects@unc.edu.

Subject's Agreement
I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate. I agree to my specimen(s) being stored with the identifying code(s).

_____ _____
Signature of Research Subject Date

_____
Printed Name of Research Subject

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent

University of North Carolina at Chapel Hill

HIPAA Authorization for Use and Disclosure of Health Information for Research Purposes

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Title of Study: Randomized Explanatory Trial of a Mediterranean Dietary Pattern Weight Loss Intervention for Primary Care Practice—also known as the DELISH (Delicious Eating for Life in Southern Homes) Study

Principal Investigator: Thomas Keyserling, MD, MPH
Mailing Address for UNC-Chapel Hill Department: CB:7110 5020b Old Clinic , CB 7110 , Chapel Hill, NC 27599 , USA

This is a permission called a "HIPAA authorization." It is required by the "Health Insurance Portability and Accountability Act of 1996" (known as "HIPAA") in order for us to get information from your medical records or health insurance records to use in this research study.

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1. If you sign this HIPAA authorization form, you are giving your permission for the following people or groups to give the researchers certain information about you (described below):

Any health care providers or health care professionals or health plans that have provided health services, treatment, or payment for you such as physicians, clinics, hospitals, home health agencies, diagnostics centers, laboratories, treatment or surgical centers, including but not limited to the UNC Health Care System and its members and affiliates (collectively, "UNCHCS"), health insurance plans, and government health agencies.

2. If you sign this form, this is the health information about you that the people or groups listed in #1 may give to the researchers to use in this research study:

Any information in your medical records that relates to your participation in this research. Our primary focus will be to review your medical records for changes in your medications, to see if you were admitted to the hospital or evaluated in the emergency room for heart attack or stroke, and if any adverse outcomes occur as a part of this research to learn about your health outcomes if evaluated by health professionals for this type of problem.

3. The HIPAA protections that apply to your medical records will not apply to your information when it is in the research study records. Your information in the research study records may also be shared with, used by or seen by collaborating researchers, the sponsor of the research study, the sponsor's representatives, and certain employees of the University of North Carolina at Chapel Hill or other affiliated entities conducting the research, or government agencies (like the FDA) if needed to oversee the research study. HIPAA rules do not usually apply to those people or groups. If any of these people or groups reviews your research record, they may also need to review portions of your original medical record relevant to the situation. The informed consent document describes the procedures in this research study that will be used to protect your personal information. You can also ask the researchers any questions about what they will do with your personal information and how they will protect your personal information in this research study.

4. If you want to participate in this research study, you must sign this HIPAA authorization form

to allow the people or groups listed in #1on this form to give access to the information about you that is listed in #2. If you do not want to sign this HIPAA authorization form, you cannot participate in this research study. However, not signing the authorization form will not change your right to treatment, payment, enrollment or eligibility for medical services outside of this research study.

5. This HIPAA authorization will not stop unless you stop it in writing.

6. You have the right to stop this HIPAA authorization at any time. You must do that in writing. You may give your written stop of this HIPAA authorization directly to Principal Investigator or researcher or you may mail it to the department mailing address listed at the top of this form, or you may give it to one of the researchers in this study and tell the researcher to send it to any person or group the researcher has given a copy of this HIPAA authorization. Stopping this HIPAA authorization will not stop information sharing that has already happened.

7. You will be given a copy of this signed HIPAA authorization.

_____ _____

Signature of Research Subject Date

_____

Print Name of Research Subject

6/8/24: The Final version of consent documents are included below:

Main consent: 3/4/22

University of North Carolina at Chapel Hill
Consent to Participate in a Research Study
Adult Participants

Consent Form Version Date: March 4, 2022
IRB Study # 19-1712
Title of Study: Randomized Explanatory Trial of a Mediterranean Dietary Pattern Weight Loss Intervention for Primary Care Practice—also known as the DELISH (Delicious Eating for Life in Southern Homes) Study
Principal Investigator: Thomas Keyserling, MD, MPH
Principal Investigator Department: Medicine-Internal Medicine
Principal Investigator Phone number: (919) 966-6081
Principal Investigator Email Address: thomas_keyserling@med.unc.edu
Funding Source and/or Sponsor: NIH National Heart, Lung, and Blood Institute (NHLBI)

Study Contact Telephone Number: 919-843-9563
Study Contact Email: kiira_lyons@med.unc.edu or thomas_keyserling@med.unc.edu

SUMMARY
Intensive weight loss programs (14 or more counseling sessions over 6 months) are recommended for patients with a body mass index (BMI) greater than 30, yet long-term weight loss is often modest and many prior weight loss programs have not focused on what we now know to be a healthy eating pattern. This study will compare a new weight loss program that focuses on a healthy eating pattern (call Med-South) with WW™ (formally Weight Watchers™), an effective and widely available weight loss program. Those who take part will be randomly assigned (like flipping a coin) to either the new weight loss program or WW™. Both programs will last for 2 years with measurement visits at the start of the study and at 4-, 12-, and 24-month follow-up.

This is a low-risk study, as both weight loss programs follow current guidelines for such programs. There may be minor pain from the blood draws at each measurement visit. Intensive weight loss programs do involve many counseling visits so taking part does require a time commitment, as described below. We expect participants in both study groups will lose weight and consider this a benefit of taking part in the study.

(Please also see pages entitled "Information about Participating in a Research Study during COVID-19." Specific information related to COVID-19 and limitations on in-person counseling or group counseling are noted in italics below. This may change over time according to updates in guidelines about COVID-19.)

Introduction:

We invite you to take part in this research project. This form tells you about the project so you can decide if you want to join this study. If you do, you can change your mind and withdraw at any time. We think you will benefit from taking part in this study, but you may not, as the purpose of research studies is to gain new knowledge that may help others in the future. There also may be risks to being in a research project and these are noted on this form. If you do not take part in this study or you start the study and then decide to stop taking part before it is done, your decision will not be a problem for your doctors or other health care providers.

What is the purpose of this study?

The purpose is to develop and test a new weight loss program that includes a major focus on a healthy dietary pattern. A healthy dietary pattern includes eating more foods with high-quality fats (vegetable oils, nuts, seeds, fish) and high-quality carbohydrates (fruits, non-starchy vegetables, whole grains, and beans) and eating fewer foods with poor quality carbohydrates (sugar sweetened beverages, refined grains, and many processed foods). The eating pattern we are testing is similar to a Mediterranean dietary pattern. We call this new weight loss program the "Med-South Weight Loss Program" because it will be tested in the southern US. To learn if the Med-South Weight Loss Program is more effective than currently available weight loss programs, we will compare it to WW™ (formally Weight Watchers™). We have selected WW™ because it is an effective weight loss program that is widely available.

You are being asked to be in this study because your Body Mass Index (BMI) was greater than 30 (when last checked at the clinic) and your doctor approved for you to take part because he or she thinks you might benefit from losing weight.

How many people will take part in this study?
There will be about 360 people in this research study.

How long will your part in this study last?
About 2 years.

What will happen if you take part in the study?
First, we mailed you the study brochure and then study staff called to confirm that you are eligible and to see if you want to take part. If so, we mailed or emailed you this consent form. Next, we will call to answer any questions about this form. After doing so, if you want to take part, we will give you instructions on how to sign this form electronically or you may sign it at your first study visit (enrollment visit). Then, we will schedule the enrollment visit.

Study surveys are completed online before the enrollment visit. We will email you a link to access the surveys by smartphone, tablet, or computer. We expect it to take about 1.5 hours to fill out all surveys that ask about your lifestyle behaviors (like eating and physical activity habits) and other questions about your health. You do not need to complete them all at one time. You may re-access the surveys using the same link. (We will call you within 24 hours before this and all study visits to review a symptom checklist related to COVID-19.)

The enrollment visit, follow-up measurement visits, and in-person counseling visits will take place at the UNC Center for Health Promotion and Disease Prevention, 1700 Martin Luther King, Jr, Blvd., Chapel Hill, NC, which is located about 5 miles north of the UNC main campus. (We will send instructions on how to get to our office.) We will ask you to fast for 9 hours and avoid caffeine for 30 minutes before the enrollment visit and the other measurement visits, but if you are unable to fast you may still participate. We will schedule these visits in the morning. At the beginning of the visit, we will invite you to empty your bladder (recommended before measuring blood pressure). If you have not already signed the consent forms online, we will start the first visit by having you sign the consent forms. Then, we will check to see if all surveys have been filled out and complete any that may not have been done. Next, we will review your current medication listed in the UNC medical record and record medications you are taking for diabetes, high blood pressure, high cholesterol, and for heart burn or stomach ulcers.

Next, we will check your weight, height, and blood pressure. Then, we will ask you to put your finger in an instrument that checks skin carotenoid levels (which tell us about how much fruit and vegetables you eat or drink). This test does not hurt and takes less than 3 minutes. After that, we will collect a blood specimen (about 2 tablespoons). We will measure total cholesterol, HDL cholesterol, triglycerides, and A1c (a test of your blood

glucose over the past 3 months). We will report the results of these tests to you and your primary care clinician. We will also do some special research blood tests to look at how what you eat impacts blood inflammatory markers. If you agree, we will also store blood for future research. (Please note: on occasion, a study phlebotomist [person who draws blood samples] may not be at our research office. If this occurs, we may ask you to stop by one of the nearby UNC phlebotomy sites, at either the ACC or Eastowne clinics, to get your blood drawn prior to your visit at our research office. If this occurs, a study staff member will meet you at the phlebotomy office to answer any questions about the study and to have you sign the consent forms, if you did not already do so online. We will provide additional compensation for this extra time, as noted below.)

There is a great deal of scientific interest in how dietary patterns may change the bacteria that live in your intestines (the microbiome) and if these changes impact weight change. So that we can learn if your microbiome changes in response to the weight loss programs, we invite participants to submit stool samples. This part of the study is voluntary. If you agree to do so, we ask you to collect and return (by mail) a stool sample within 2 weeks of the enrollment visit and the other study visits. Study staff will go over the instructions for collecting these samples at your first visit.

It will take about 30-45 minutes to complete the measures outlined above and to collect your blood sample.

After we collect the blood sample, study staff will randomly assign you (like flipping a coin) to receive either the Med-South Weight Loss Program or WW™. If you are assigned to the Med-South Weight Loss Program, you will receive your first counseling session, which should take 45-60 minutes. If assigned to WW™, we will give you instructions on how to get started with this program, which should take about 15-30 minutes. *(Note, these sessions will take place in a large conference room—you will be seated more than 10 feet away from study staff.)* If you bring your smartphone to the visit, we will help you download the WW™ App. Also, whichever group you are in, you will be encouraged to do moderate physical activity, like brisk walking, which is recommended for all Americans.

Please note, WW™ is a safe and effective program that is considered a standard for community-based weight loss programs. If you are randomized to this program, we encourage you to engage with the program and take full advantage of what it has to offer. We do not know if the new program we have developed is better than WW™. That is what we hope to learn in this study. If it turns out the Med-South Program is better, then components of the Med-South Program may be added to other weight loss programs in the future.

Med-South Weight Loss Program

Most weight loss programs offer weekly one-on-one or group counseling sessions for 16-20 weeks. The Med-South Weight Loss Program is different and is given in 3 phases. The program begins with **Phase I**, a 4-month lifestyle phase that focuses on the "basics" of healthy eating rather than weight loss. Over the next 8 months in **Phase II**, we focus on weight loss, followed by a year-long (**Phase III**) phase to help you maintain weight loss. In Phases I, the main counseling sessions are given monthly, followed by check-in phone calls 1-2 weeks later. In

Phase II, the main counseling sessions will occur weekly for the first 8 weeks, then monthly for the remaining 6 months, depending on your progress. There are also check-in phone calls--the number will vary based on your progress. During Phase III, there are 2 main visits and follow-up phone calls. More details about these visits are in the table below.

Some of your counseling visits will be face-to-face with your counselor and some by phone. Only one member of a family may join this study, but other family members are invited to take part in face-to-face and phone counseling sessions. *(As of September 2020, due to COVID-19 only one other family member or friend may come with you to in-person visits.)* The face-to-face format will be required for a total of 5 visits – the *first visit* in each of the 3 phases (right after study measurements at enrollment, and 4 and 12 months), 2 months after starting the weight loss program in Phase II, and mid-way during Phase III (about 18 months after starting the Program). *(As of September 2020, we will allow other visits to be done in person if that is the preference of the study participant. Otherwise, the other visits will be done by phone or videoconferencing.)* The other sessions may be done by phone/videoconference or in-person. During Phases II and III, when you come to our office for a face-to-face counseling session, we will also check your weight.

During face-to-face sessions, you and the counselor will use a web-based program or the paper format to review educational materials, select dietary goals, and list first steps to reach these goals. If the phone format is used for major counseling sessions, you may view the educational content online or use your paper version. The program also includes brief telephone calls to check on progress towards goals selected at previous sessions and provide support for lifestyle change. The number of phone calls you get will depend on if you are meeting your personal weight loss goals in Phase II or keeping the weight off in Phase III. The table below has more information.

Phases	**# Contacts**	**Contact Length**	**Estimated Total Contact Time**

Phase I	• 8 total
	  ○ 4 core sessions: the first must be in-person; choice of in-person or phone for all others
	  ○ 4 follow-up phone calls
		• Core session = 45-60 min.
		• Follow-up call = 15 min.
			4 - 5 hours

Phase II	• 14 core sessions: the first and a visit about 2 months later must be in-person; choice of in-person or phone for all others. • 6-12 follow-up phone calls	• Core session (in-person) = 45-60 min. • Core session (phone) = 30-45 min. • Follow-up call = 20-30 min.	8.7 – 14 hours (core) 4.7 – 9.5 hours (Follow-up)
Phase III	• 2 core sessions (both in-person)	• Core session (in-person) = 45-60 min.	1.25 – 2 hours (Core) 3 – 8 hours (Follow-up)

	• 12-24 follow-up phone calls (1-2 per month)	• Follow-up call = 15-20 min.	
2-Year Program TOTAL	**44 – 60 Contacts**	**--**	**21.7 – 38.5 hours**

If you agree, we may audio-record a few counseling sessions for quality improvement purposes (to check on how our counselors are doing and provide feedback on areas needing improvement). These recorded sessions will be kept as electronic files but without information that could be used to identify you (other than your voice).

WW™ Weight Loss Program

If you are randomized to WW™, you will have access to both the workshop and digital components of the WW™ Program for 2 years. WW offers in-person coaching and community-based learning through weekly Workshops at WW™ Studios. The Workshop component allows for attending weekly group meeting at a WW™ studio (local WW™ office). [*As of September 2020, due to COVID-19, the workshop component will be available in a virtual videoconferencing [Zoom™] format in most locations, but may be available for in-person group sessions at some locations (where sessions are given in a large room with limited attendance and following North Carolina guidelines for wearing masks and social distancing.)]*

The Digital component can be accessed using the WW™ website or a smartphone App. The digital tools available in the WW™ Digital program include food tracking (either manually or with bar code scanning), progress charts, lifestyle coaching with 24/7 chat with a WW Coach, ability to track activity (manually or by syncing a fitness tracking device), incentives for behavior change (WellnessWins), recipes, and even local restaurant recommendations using GPS. You will also have access to Connect, a digital community for WW™ members. Study staff will provide basic instructions on how to use the WW™ digital resources.

The WW™ Program uses "SmartPoints" assigned to foods based on energy content and nutritional value, allocating a certain number of points to users daily based on their starting weight, weight loss goals, age, and sex. You'll receive a personalized SmartPoints budget made up of Daily SmartPoints, plus some extra Weekly SmartPoints for those days when you need a "cushion."

If you are assigned to the WW™ Program, you get to decide how many workshops to attend and how often to use the digital program. You can decide to not attend the workshops and only use the phone App and/or website. *(As noted above, as of June 2020, due to COVID-19, the workshop component will be in a virtual videoconferencing [Zoom™] format, until further notice.)* At the 4 month follow-up visit, we will check to see if you have been using the WW Program. If not, we will ask if you would like study staff to check in with you about using this Program.

Follow-up measurement visits

About 4, 12, and 24 months after starting the study, we will ask you to return for follow-up measures, which will be like those collected at study enrollment. We will ask you to fill out surveys online before this visit. It will take about 1 to 1.5 hours to fill out the surveys and 30 minutes for the measurement visits. Please note that for us to understand if the Med-South Weight Loss Program is effective, we must carefully measure many study outcomes. Most of these outcomes are measured by questionnaire. The amount of blood work drawn for measurement is like that taken at routine office visits when several tests are ordered (about 2 tablespoons at baseline and 12 months; and 1.5 tablespoons at 4 and 24 months). The stool test is optional. As outlined below, we will compensate for your time spent on measurement at a rate of $20 to $30 dollars per hour. And we thank you in advance for your willingness to complete this very important part of the study. **(Please note: on occasion, a study phlebotomist [person who draws blood samples] may not be at our research office. If this occurs, we may ask you to stop by one of the nearby UNC phlebotomy sites, at either the ACC or Eastowne clinics, to get your blood drawn prior to your visit at our research office. If this occurs, either study staff will meet you at the phlebotomy office or we will drop off the collection tubes in advance and ask you to bring them to the office. We will provide additional compensation for this extra time, as noted below.)**

Contacting you for follow-up visits
We will call you up to 3 times over a 4-week period during regular work hours and after hours. We may also send up to 2 texts and/or emails if you agreed to receive texts or emails while taking part in this study. If we cannot reach you, we will send a letter and invite you to contact us if want to continue in the study or if you want to stop, to let us know why. Again, it is fine to stop taking part in this study at any time.

Will I be informed about the study's findings?
We will inform all who take part about the study's findings. If the Med-South Weight Loss Program results in greater weight loss, we will make the Med-South Program materials available to those who received the WW™ Program.

Should I take part in this study?
Prior research indicates that for weight loss studies to be effective, they must offer an intensive intervention, defined as at least 14 sessions over a 6-month period. That is why the Med-South Program includes many contacts and why WW™ suggests frequent contact with their program. So, you need to ask yourself if you are willing to make this type of commitment to a weight loss program. If you are, we welcome you to this study! We will do all we can to accommodate your schedule or any special needs you may have as you take part in the weight loss programs and return for measurement visits.

What are the possible benefits from being in this study?
We think you may benefit from being in this study by improving your lifestyle and losing weight. However, you may not benefit from being in this study.

What are the possible risks or discomforts involved from being in this study?

The possible risks and discomforts from being in this study are few and are listed below.

- We do not think there is risk to you from the dietary advice given as part of the Med-South Program or WW™.
- Eating less is a part of standard weight loss programs. If you do not eat enough, you could lose weight too fast. By asking you to check your weight often, the weight loss programs in this study will let you know if and when you are losing weight too fast.
- Although doing more physical activity is not the main focus, both weight loss programs will recommend you do moderate physical activity. Those who increase their level of physical activity may experience minor muscle pain (this is common, affecting more than 50 in a 100 people), but this type of activity rarely (fewer than 1 in a 100) causes serious health problems such as chest pain or asthma.
- For those with diabetes, losing weight and reducing carbohydrate in the diet can lead to lower blood sugar, including hypoglycemia. This has occurred in less than 1 in a 100 people in our past studies. We will provide those with diabetes information on how to reduce the risk of low blood sugar.
- For those with high blood pressure, losing weight can lead to lower blood pressure, which can cause dizziness and even falls. Adverse outcomes related to low blood pressure are very rare in weight loss studies, occurring in less than 1 in a 100 people. Typically, the blood pressure is lowered slowly with weight loss, allowing your doctor time to observe the lower blood pressure and reduce your blood pressure medicine.
- A blood sample will be collected by trained staff. The risk of minor pain is very common (in more than half of people). Bruising does not happen often (about 1-10 of every 100 persons) and the risk of infection or fainting is rare (fewer than 1 in 100).
- In all studies, there is a very slight chance of loss of privacy (that is, others may see your study information). As stated below, we will do all we can to make sure this does not happen.

Also, there may be other risks we did not list here. You should report to the research team any problems that may be due to this study.

What if we learn about new findings or information during the study?

You will be given any new information gained during the study that might affect the risk of taking part in this study.

How will information about you be protected?

Your study bloodwork for routine tests (cholesterol levels and A1c) will be stored with your name as this will be sent to a commercial lab for analysis (LabCorp). These samples are typically thrown away 5-7 days after collection. Your study surveys and bloodwork for the inflammatory markers will be stored with your study ID number and your first and last initial, but NOT with your name (we call this de-identified data). No one other than study staff will be able to connect your name and study ID as we will follow standard procedures to protect the privacy of research data.

We may use your de-identified data, as described above, in future research without additional consent. However, in some cases, the Institutional Review Board (called IRB and described

below) may require that you be re-contacted and asked for your consent to use your data in a specific research study. You have the right, at that future time, not to participate in any research study for which your consent is sought.

Participants will not be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by agents of the University or research sponsors for purposes such as quality control or safety.

By signing this informed consent document, you agree that some of the information generated by participating in this study and/or a copy of the consent form may be included in your medical record and that this information may be viewed by other physicians or caregivers who provide healthcare services to you. This will allow the doctors caring for you to know what tests you may be receiving as a part of the study and know how to take care of you if you have other health problems or needs during the study.

What is a Certificate of Confidentiality?

This research is covered by a Certificate of Confidentiality. With this Certificate, the researchers may not disclose or use information, documents or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings in the United States, for example, if there is a court subpoena, unless you have consented for this use. The Certificate cannot be used to refuse a request for information from personnel of a federal or state agency that is sponsoring the study for auditing or evaluation purposes.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law, such as mandatory reporting requirements for child abuse or neglect, disabled adult abuse or neglect, communicable diseases, injuries caused by suspected criminal violence, cancer diagnosis or benign brain or central nervous system tumors or other mandatory reporting requirement under applicable law. The Certificate of Confidentiality will not be used if disclosure is for other scientific research, as allowed by federal regulations protecting research subjects or for any purpose you have consented to in this informed consent document.

What will happen if you are injured by this research?

It is not likely that you will be injured by this research, but all research involves a chance of injury. If a medical problem occurs, the researchers will help you get medical care, but costs for this care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for injuries or medical care. However, by signing this form, you do not give up any of your legal rights.

What if you want to stop before your part in the study is complete?
You can withdraw from this study at any time, without penalty. The research team also has the right to stop your participation at any time. This could be because you have had an unexpected reaction, or did not follow instructions, or because the entire study has been stopped.

Will you receive anything for being in this study and will it cost you anything to take part?
You will receive the weight loss program and lab work free of charge. You will receive $60 payment for your time devoted to study measures at the start of the study and at 4-, 12-, and 24-month follow-up. The payment rate is $20-30/hour. If you complete all measurement visits, you will receive a total of $240. In addition, you will receive $30 reimbursement for each stool specimen you submit and $20 reimbursement if we you have your blood work done at one of the UNC phlebotomy offices.

We will calculate the one-way distance from your home address to our research office and will reimburse mileage for measurement visits as below. Note, there is *no reimbursement for mileage* if you attend a WW™ workshop or if you come in for a Med-South Weight Loss Program counseling visit that does not include a measurement visit (measurement visits are: enrollment visit and 4-, 12-, and 24-month follow-up visits). Parking is free. All reimbursement will be by gift card.

Mileage reimbursement rate:

- Less than 10: $0
- 10-19 miles: $10
- 20-29 miles: $20
- 30-39 miles $30
- 40-49 miles $40
- 50-59 miles $50
- 60 or more $60

Who is sponsoring this study?
This study is funded by the National Heart, Lung, and Blood Institute (NHLBI). This means the research team is being paid by NHLBI for doing the study. The researchers do not have a financial interest in the final results of the study.

What if you are a UNC employee?
Taking part in this research is not a part of your University duties and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have questions about the study (including payments), complaints, concerns, or if a research-

related injury occurs, you should contact the researchers listed on the first page of this form.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What if you have questions about your rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Participant's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

I also agree to submit stool samples as part of my participation in this study.

____ yes

_____no

_____ _____
Signature of Research Participant Date

_____
Printed Name of Research Participant

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent

Stored specimens updated 3-2-25

University of North Carolina at Chapel Hill
Consent for Storing Biological Specimens <u>With</u> Identifying Information

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Consent Form Version Date: 3-2-2020
IRB Study # 19-1712
Title of Study: Randomized Explanatory Trial of a Mediterranean Dietary Pattern Weight Loss Intervention for Primary Care Practice—also known as the DELISH (Delicious Eating for Life in Southern Homes) Study
Principal Investigators: Thomas Keyserling, MD, MPH
Principal Investigator Department: Medicine-Internal Medicine
Principal Investigator Phone number: (919) 445-6794
Principal Investigator Email Address: thomas_keyserling@med.unc.edu
Funding Source and/or Sponsor: NIH National Heart, Lung, and Blood Institute (NHLBI)

Study Contact Telephone Number: 919-843-9563
Study Contact Email: kiira_lyons@med.unc.edu

CONCISE SUMMARY

See study consent form for summary of the overall study. This form provides information about stored specimens that may be collected as part of this study. Providing stored specimens for the study is optional. As outlined in the study consent form, blood samples will be obtained at enrollment and at 4, 12, and 24 month follow-up. If you agree to allow the researcher to store your blood specimens for future research, an additional tube of blood (about 2 teaspoons) will be collected at the enrollment visit and 12 month follow-up visit. Research using your stored specimens may help the researchers better understand how your body responded to the weight loss interventions. This research will also allow us to understand if your response to the intervention is related to your genes.

The following information about research related to use of stored specimens is covered in study consent form:

- **<u>What are some general things you should know about research?</u>**
- **<u>How will information about you be protected?</u>**
- **<u>What is a Certificate of Confidentiality?</u>**
- **<u>What will happen if you are injured by this research?</u>**
- **<u>Who is sponsoring this research?</u>**
- **<u>What if you have questions about this research?</u>**
- **<u>What if you have questions about your rights as a research subject?</u>**

<u>What is the purpose of this specimen repository or "biobank?"</u>
Research with blood, tissue or body fluids (specimens) can help researchers understand how the human body works and help answer research questions about how the body responds to different weight loss programs. It is possible that this type of research my help researchers improve weight loss interventions and even develop new products, such as drugs. This type of research includes genetic research. Sometimes researchers collect and store many specimens together and use them

for different kinds of research, or share them with other scientists; this is called a specimen repository or "biobank."

The purpose of this particular repository or biobank is to have specimens that may be used to better understand weight loss interventions. Future research done with these specimens may include genetics research. Information on genetics research, including risks, is provided in the next section.

Information on genetics research and risks of this research

As genes are so important to our health, it is very common now for research studies to include genetic tests as we may do with stored specimens collected for this study. If done, the major focus of the genetics research would be to see if genes or groups of genes help us to better understand how you responded to the weight loss programs. If you give a blood sample for genetics research, it will become the property of the UNC Chapel Hill and the sample may be kept for years. If you decide you want to withdraw from the genetics part of this study, contact the researcher listed above. The primary risk of genetic research is loss of privacy and as noted on this form, we will take all routine steps to reduce this risk. That said, it is important for you to be aware of the following:

- A Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.
- The National Institutes of Health (NIH) has established a national database that will hold information from many individuals across the country, including medical information and genetic information. If information about you is sent to this national database, it will not be identified (that is, no one can tell whose information it is). This information may include sequencing your entire genome (all of your genes). Also, access to this information will be controlled and limited to other researchers.

Will you receive results from the genetics research?

Most genetics research is not expected to yield new information that would be meaningful to share with you personally. There are no plans to re-contact you or other participants with information about research results. The use of your samples may result in commercial profit. You will not be compensated for the use of your samples.

In a few participants, however, we may find genetic variants that are not related to the purpose of this study, but that are related to other medical conditions. These variants are rare and we expect to find them in fewer than 5% of the people who take part in this study.

- If you have one of these variants, it suggests that you have a serious medical condition that can be treated OR that you have a high risk for a future medical problem that can likely either be prevented or more successfully treated if doctors know about it ahead of time.
- An example of one of these conditions is hereditary cancer predisposition. If you have a condition like this, your doctor may recommend special screening to look for early cancers that would be more easily treated, or in some cases preventive surgery to reduce the risk of developing cancer.
- If you have one of these variants, your children would be at risk to have inherited it from you. In addition, it may have been inherited from one of your parents, and others in the family (siblings, aunts/uncles, cousins etc.) might also be at risk to have the variant.

- In the event that your genetic analysis suggests you have one of these variants, we will ask you for a separate sample using a saliva kit so that the finding can be confirmed by the clinical laboratory and reported to you by a clinical Genetic Counselor. The results will be included on a clinical laboratory report and it will become part of your UNC medical record.
- The genetics team may make health care recommendations for you and your family based upon the genomic sequencing results. These recommendations might include other clinic visits and evaluations for you and other relatives. These evaluations can provide important information about their need for medical care. These other visits, tests, and evaluations are not part of this study and will not be paid for by the study.
- The American College of Medical Genetics and Genomics recommends that, when genomic sequencing is done, these variants should be looked for, interpreted, and reported.

How will the specimens be collected?

At the baseline visit and at the 1 year visit, 10 ml (2 teaspoons) of blood will be collected. This will be done during the same blood draw as other study tests so this will NOT involve another needle stick. The specimen will be labelled with a study number only.

What will happen to the specimens?

The specimens will stored in a freezer on the campus of UNC-Chapel Hill. The code linking the number of on the specimen to your identifying information will be stored on a password protected computer. Only study researchers will have access to the code linking the study number of the tube to your identifying information.

What are the possible benefits to you?

Benefits to you are unlikely. However, as outlined above, if genetic variants are found that suggest you have a serious medical condition that can be treated OR that you have a high risk for a future medical problem that can likely either be prevented or more successfully treated if doctors know about it ahead of time, we will contact you with this information. This information may be beneficial to your health.

What are the possible risks or discomforts involved with the use of your specimens?

As the blood will be drawn at the same time as the routine study blood (during the same "stick") there are not additional risks associated with collecting this specimen.

There is a risk of breach of confidentiality. If this research involves genetics, there is also a potential risk for some of your relatives and other members of your ethnic group, since they share some of your genetic makeup.

Will researchers seek approval from you to do future studies involving the specimens?

By signing this consent form, you are giving your permission for researchers to use your specimens as described above. Current and future research is overseen by a committee called the Institutional Review Board (IRB). The role of the IRB is to protect the rights and welfare of research participants. We may use de-identified data and/or specimens from this study in future research without additional consent. However, in some cases, the IRB may require that you be

re-contacted and asked for your consent to use your specimens in a specific research study. You have the right, at that future time, not to participate in any research study for which your consent is sought. Refusal to participate will not affect your medical care or result in loss of benefits to which you are entitled.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from having your specimen collected. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. However, by signing this form, you do not give up any of your legal rights.

Will you receive results from research involving your specimens?
Most research with your specimens is not expected to yield new information that would be meaningful to share with you personally. There are no plans to re-contact you or other subjects with information about research results, except as outlined above.

Can you withdraw the specimens from the research repository?
If you decide that you no longer wish for the specimens to be stored, you should contact the researchers on the front page of this form. It is best to make your request in writing.

Any analysis in progress at the time of your request or already performed prior to your request being received by the researcher will continue to be used as part of the research study. Once the researchers have been notified, your remaining specimens would be destroyed. If you do not make such a request, the specimens may be stored forever. The researchers may choose to destroy the specimens at any time.

Will there be any cost to you for storage of the specimens?
There will be no cost to you for the storage and use of the specimens for research purposes.

What if you have questions about your rights as a research subject?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously if you wish, the Institutional Review Board at 919-966-3113 or by e-mail to IRB_ subjects@unc.edu.

Subject's Agreement
I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate. I agree to my specimen(s) being stored with the identifying code(s).

_____ _____
Signature of Research Subject Date

_____
Printed Name of Research Subject

_____ _____
Signature of Research Team Member Obtaining Consent Date

_____
Printed Name of Research Team Member Obtaining Consent

HIPAA Authorization updated 3/2/20

University of North Carolina at Chapel Hill

HIPAA Authorization for Use and Disclosure of Health Information for Research Purposes

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IRB Study # 19-1712

Title of Study: Randomized Explanatory Trial of a Mediterranean Dietary Pattern Weight Loss Intervention for Primary Care Practice—also known as the DELISH (Delicious Eating for Life in Southern Homes) Study

Principal Investigator: Thomas Keyserling, MD, MPH
Mailing Address for UNC-Chapel Hill Department: CB:7110 5020b Old Clinic , CB 7110 , Chapel Hill, NC 27599 , USA

This is a permission called a "HIPAA authorization." It is required by the "Health Insurance Portability and Accountability Act of 1996" (known as "HIPAA") in order for us to get information from your medical records or health insurance records to use in this research study.

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1. If you sign this HIPAA authorization form, you are giving your permission for the following people or groups to give the researchers certain information about you (described below):

Any health care providers or health care professionals or health plans that have provided health services, treatment, or payment for you such as physicians, clinics, hospitals, home health

agencies, diagnostics centers, laboratories, treatment or surgical centers, including but not limited to the UNC Health Care System and its members and affiliates (collectively, "UNCHCS"), health insurance plans, and government health agencies.

2. If you sign this form, this is the health information about you that the people or groups listed in #1 may give to the researchers to use in this research study:

Any information in your medical records that relates to your participation in this research. Our primary focus will be to review your medical records for changes in your medications, to see if you were admitted to the hospital or evaluated in the emergency room for heart attack or stroke, and if any adverse outcomes occur as a part of this research to learn about your health outcomes if evaluated by health professionals for this type of problem.

3. The HIPAA protections that apply to your medical records will not apply to your information when it is in the research study records. Your information in the research study records may also be shared with, used by or seen by collaborating researchers, the sponsor of the research study, the sponsor's representatives, and certain employees of the University of North Carolina at Chapel Hill or other affiliated entities conducting the research, or government agencies (like the FDA) if needed to oversee the research study. HIPAA rules do not usually apply to those people or groups. If any of these people or groups reviews your research record, they may also need to review portions of your original medical record relevant to the situation. The informed consent document describes the procedures in this research study that will be used to protect your personal information. You can also ask the researchers any questions about what they will do with your personal information and how they will protect your personal information in this research study.

4. If you want to participate in this research study, you must sign this HIPAA authorization form to allow the people or groups listed in #1on this form to give access to the information about you that is listed in #2. If you do not want to sign this HIPAA authorization form, you cannot participate in this research study. However, not signing the authorization form will not change your right to treatment, payment, enrollment or eligibility for medical services outside of this research study.

5. This HIPAA authorization will not stop unless you stop it in writing.

6. You have the right to stop this HIPAA authorization at any time. You must do that in writing. You may give your written stop of this HIPAA authorization directly to Principal Investigator or researcher or you may mail it to the department mailing address listed at the top of this form, or you may give it to one of the researchers in this study and tell the researcher to send it to any person or group the researcher has given a copy of this HIPAA authorization. Stopping this HIPAA authorization will not stop information sharing that has already happened.

7. You will be given a copy of this signed HIPAA authorization.

_____ _____

Signature of Research Subject Date

_____

Print Name of Research Subject

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Below also appears in Section 5.5. We have received a waiver from the IRB to obtain verbal consent for the collection of questionnaire data from those who do not want to sign consent via the e-consent option.

Step 6—Contacting participants identified in Step 5 to assess eligibility and interest (See PDF of this document)

- Mail information brochure and cover letter to potential participants identified as outlined above and request that within one week, those who 1) know they are interested or 2) know that they are NOT interested send us an email or call to provide this information. Place those who express interest on our call list.
- Approximately 10 days after mailing, start calling those who we do not hear from. Our call protocol is as follows:
    - We will call up to 5 times over a 2 week period. We will attempt 2 calls during regular work hours (8:30 to 5:30 on weekdays) and 3 after hours, including Mon-Thurs evening between 5:31 and 9:00 pm and on Saturday calling between 8:30 and 5:30 pm.
    - We will leave up to 2 phone messages.
- During eligibly calls, data are entered into the REDCap eligibility questionnaire. This form has text for the phone call.
- If a potential participant is interested and eligible, staff will either mail or email the consent forms to this individual and an appointment will be made for the consent phone call in about 1 week.

Step 7—Study staff updates the Excel data base based on eligibility phone call.

- Status variable
    - 1 indicates potential participant agrees to be contacted again for Consent Phone call.
    - 2 indicates potential participant contacted, but not interested. Identifying data is removed. (Name, DOB, address, and phone #).

- 3 indicates potential participant contacted and is interested, but not eligible. Identifying data is removed. (Name, DOB, address, and phone #).
- 4 indicates potential participant never contacted by phone. Identifying data is removed. (Name, DOB, address, and phone #).

Step 8—Consent phone call (See PDF of this document)

- At this phone call, key components of the consent form are reviewed in detail to insure that the potential participant understands what participation entails. During the phone call, the "Stored Specimens with Identifiers" and "HIPAA Authorization" are also reviewed. It the potential participant agrees to sign consent form via e-consent, instructions are given on how to do so. If the potential participant prefers to sign at the enrollment visit, then verbal consent to complete baseline questionnaires before the enrollment visit will be obtained, as approved by the IRB.
- Instructions for completing baseline forms, on-line or by phone, are given and plans to complete these forms are made accordingly. An appointment date is set for the baseline visit.
- Parameters for contacting the patient are the same as for the eligibility phone call outlined in Step 6.

Enrollment visit and randomization: At the enrollment visit, all questions will be answered about the study and those who did not sign the consent forms on-line will sign the consent form. Upon completion of baseline measures the participant will be ready for randomization. The research assistant will use a secure web-portal to ascertain randomization assignment

10.1.2 STUDY DISCONTINUATION AND CLOSURE

Given the low risk nature of the study, we do not anticipate stopping for adverse outcomes.

The DSMC may stop the study based on their assessment of "futility" attributed to poor participant enrollment.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and

pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the <specify name of Data Coordinating Center>. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by this study will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the <specify name of Data Coordinating Center>.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality
To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Most issues related to stored specimens are outlined on the Stored Specimen Consent Form in Section 10.1.1.1. Specifically, we will:

- Store specimens on the campus of the UNC-Chapel Hill. Blood specimens will stored at -80 C in the lab of Steve Hursting, PhD, Gillings School of Global Public Health.
- Data will be stored on secured servers administered by UNC-Chapel Hill IT.
- At the time of this protocol preparation, data and specimens will be stored indefinitely.
- Genetics testing may be done as outlined on the consent form.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor or Independent Safety Monitor. Update table heading to remove non-relevant role.

Principal Investigator	**Medical Monitor or Independent Safety Monitor**
Thomas C. Keyserling, MD, MPH *Professor of Medicine* *Department of Medicine* *Division of General Medicine and Clinical Epidemiology* *School of Medicine* *Adjunct Professor of Nutrition* *Gillings School of Global Public Health*	*Wayne Rosamond, PhD* *Professor of Epidemiology* *Gillings School of Global Public Health*
UNC-Chapel Hill	*UNC-Chapel Hill*
Manning Drive *Chapel Hill, NC 27599*	*137 East Franklin Street, Suite 306* *CB# 7435* *Chapel Hill, NC 2751*
919-445-6794	*919-962-3230*
jato@med.unc.edu	*wayne_rosamond@unc.edu*

This single site study has 2 primary committees

- Operations Committee: Includes MPIs, Project Director, and will RAs as appropriate. Meets weekly.
- Co-I Committee: Includes co-investigators and meets as appropriate to discuss major study protocol issues and later to review and interpret the data.

Oversight Committee

- Data Safety Monitoring Committee: Meets every 6 months while study is in the field.

10.1.6 SAFETY OVERSIGHT

Safety oversite is provided by a data safety monitoring committee. The charter, dated 10/29/19 is below:

DSMC Charter

The investigators believe the interventions (Med-South Weight Loss Program and Augmented Usual Care, which is Weight Watchers) and measurement protocols pose minimal risk to participants. Because of this study's low risk status, the data safety monitoring plan focuses on careful monitoring of the study's progress as well as adverse events.

The Data Safety Monitoring Committee (DSMC) will be comprised of:

- The principal investigators: Thomas C. Keyserling, MD, MPH and Carmen Samuel-Hodge, PhD, RD
- The project director: Kiira Lyons, MA
- Study biostatistician: Daniela Sotrez-Alvarez, DrPH
- Three voting impartial members including one primary care clinician:
    - Wayne Rosamond, PhD, chair
    - Kimberly Truesdale, PhD
    - Katrina Donahue, MD, MPH

Key personnel involved with the logistics of participant enrollment, participation, and follow-up will meet regularly (usually weekly) to review, among other things, progress on accrual, follow-up, and adverse events. They will then prepare the following reports for the DSMC:

Data Type	Frequency of Review
Subject accrual (including graphic of projected versus actual monthly enrollment)	Weekly, with **monthly** summary reports for Chair of the DSMC.
Adverse events	These will be reported as they occur to the IRB with **monthly** reports to the Chair of the DSMC. Any potentially study related death or severe and unexpected adverse event will be reported to the Chair of the DSMC within 1 working day.
Adherence with treatment	For the intervention group, study process measures will be collected by the web-based intervention program as well as monitoring checklists completed by the interventionist and audio recordings of up to 20% of sessions during the 2-year intervention. For the augmented usual care group, process measures will be assessed by questionnaire at follow-up measurement visits and through a data sharing agreement with Weight Watchers (WW). These data will be reviewed **semi-annually** at the DSMC meetings.
Follow-up rates for data collection	Weekly, with **monthly** summary reports prepared for the Chair of the DSMC.

(including the number of subjects eligible for and completing follow-up)	
Stopping rules with regard to benefit	Not applicable, as intervention is designed to promote weight loss during a 24-month period and lifestyle change even without weight loss is likely beneficial.
Stopping rules with regard to statistical power and adverse events	**Semi-annual** assessment by DSMC. The DSMC will review subject accrual for futility and adverse events for compelling evidence of harm and will address appropriately.

Operational definition of futility with regard to recruitment: Less than one half of the anticipated sample size enrolled during the enrollment period. This may be modified by the voting members of the DSMC.

Meetings and responsibilities of the DSMC: Prior to enrollment, the DSMC will meet to review all protocols that may have a bearing on subject accrual or safety. The DSMC will subsequently meet every 6 months until completion of the study. In addition, the PIs of the study or the Chair of the DSMC may convene additional meetings as needed. The primary role of the DSMC will be to monitor study data as outlined in the table above. The committee will also assist with any necessary modifications of protocols to address unexpected problems with subject accrual, subject attrition, or adverse events.

Measurement and reporting of adverse events (AEs): The study team will monitor adverse events that include, but are not limited to the following: deaths, hospitalizations, emergency room visits, hypoglycemia (defined as blood glucose < 60 mg/d with symptoms), and weight loss greater than 10 pounds per month. We will specifically inquire about these adverse events at all follow-up measurement visits and review medical records to confirm as appropriate (permission granted through HIPAA waiver). The PIs will be responsible for completing an AE report when a reportable adverse event is recognized and will submit this report to the UNC IRB. The UNC IRB definitions, standards, and forms will be used for reporting AEs. Also, at measurement visits, we will inquire about angina, myocardial infarction, transient ischemic attack, and stroke.

Approval of study phases: The intervention will be delivered in 3 phases over 24 months by research staff: Phase I (4 months) focuses on adopting a Med-style dietary pattern; Phase II (8 months) on weight loss; and Phase III (12 months) on weight loss maintenance. In our NIH application, we noted we would continue with intervention refinement until shortly before going to the field with each phase. This will allow us to keep up with the literature and be up-to-date at the outset of each phase. Accordingly, we will seek IRB and DSMC approval for each Phase as outlined in the table below:

Phase	IRB Approval	DSMC Approval

Phase 1 (first 4 months)	10/2/19	Nov, 2019
Phase 2 (next 8 months)	June, 2020	June, 2020
Phase 3 (next year)	June, 2021	June, 2021

10.1.7 CLINICAL MONITORING

N/A.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Milestone: Data Completeness and Quality Monitoring Reporting Plan
Date: 1/27/20
Version: 2.0

This document outlines the data completeness and quality and monitoring plan for this study. As outlined below, data will be stored in identified and de-identified data sets. The overall data management plan has been approved by the UNC IRB and the study's DSMC.

The table below outlines sources of data, where it will be stored, and aspects of data management related to data quality and security. The rows of the tables are organized by the chronological sequence of anticipated data acquisition.

The primary data collection and management program with be REDCap as administered by the NC TraCS. Links to relevant websites are provided below.

- REDCap: *https://tracs.unc.edu/index.php/services/informatics-and-data-science/redcap*
    - REDCap includes software to collect confidential survey data via email link sent to participants. In this study, data instruments used for data collection in this fashion are called "surveys."
    - REDCap data collection instruments used only by research staff to collect study data are called "forms."
    - All REDCap forms and surveys will include appropriate data entry ranges and skip patterns. These forms and surveys will be thoroughly vetted during our REDCap "development" phase and before transitioning to "production" phase.
- NC TraCS: *https://tracs.unc.edu/*

Correcting confirmed errors in the data.

- The data manager and Dr. Keyserling will be responsible for making corrections.
- A log of all corrections/edits will be maintained.

The table includes the following columns:

- Type and use of data: indicates intended use of the data.
- Data source: indicates source of the data.
- Data storage: indicates where the data are stored. All UNC servers noted below are password protected and adhere to security standards as outlined by the UNC IRB. Abbreviations include:
    - NC TraCS: UNC Translational and Clinical Sciences Institute.

    - HPDP: UNC Center for Health Promotion and Disease Prevention.
    - Sheps: Cecil G. Sheps Center for Health Services Research.
    - CSCC: UNC Collaborative Studies Coordinating Center.
- Identified (Indt.): indicates if identifiers are included with the data.
- Data Review/Other Comments: Outlines how the data will be reviewed and provides other comments as appropropriate. Data collected by REDCap forms and surveys will be reviewed by the data manager or his designee, at a weekly (but no longer than 2 week) interval. Incomplete data will be identified and reviewed by the Project Manager and/or MPIs to determine if additional effort should be directed towards collecting these data. If a major or key data component is missing, efforts will be made to collect this data in a timely fashion. For example, if a participant skips several pages on a survey, we will contact the participant to complete this survey.
- Most data are collected at baseline and 4, 12, and 24 months follow-up.

Type/Use of Data	Data Source	Data Storage	Ident.	Data Review/Other Comments
Data from the electronic medical record	NC TraCS data warehouse	• NC TraCS server • HPDP server	yes	These data, extracted from the data warehouse utilized by NC TraCS, will be provided in an Excel format for each primary care clinician at participating study sites. The programming used to identify appropriate patients in the data warehouse will be tested at each practice against data prepared from the population feature of the electronic health record. Output will be carefully inspected by research staff for completeness before it is sent to providers who must approve participation of their patients in this study.
Data for providers to review regarding participation of their patients	Primary care clinicians	HPDP server	yes	Providers will either be sent a link to a password protected Excel file with a listing of their patients who meet basic study inclusion criteria. They will be asked to review and note the patients who they refer to the study to receive an intensive multimodal weight loss program.
Eligibility data	From participants, collected by phone by research staff	REDCap server	yes	Data review: weekly, as outlined above.

Consent forms	Participants	• For consent completed on-line, REDCap server	yes	Research staff insure that consent documents are signed after all questions are answered.
Participant study data collected using REDCap forms and surveys—electronic questionnaires	Participants	REDCap server	yes	Surveys and forms will have PT-ID# and first and last initial. Data will be collected via phone for those who do not want to complete online. Data review: weekly, as outlined above.
Willett Food Frequency Questionnaire	Participants	• Data collected using REDcap version • At Harvard School of Public Health	no	Data sent to Harvard is de-identified.
Anthropometrics, blood pressure, skin carotenoids	Participants	REDCap server	yes	Data entered by research field staff from instruments used for these assessments. Note special protocol for primary outcome variable, body weight. Data review: weekly, as outlined above. • For assessment at data collection time points, weight is assessed 2 times. If difference between weights is 1 pound or greater a third assessment is performed. For analysis, weights are averaged, using the 2 weights that differ by less than a pound. • For follow-up assessments, a second member of the research staff or clinical staff must observe data entry and initial that they have done so.
"Clinical" blood work	Participants	• At LabCorp per storage of routine lab work. • REDCap	yes	Data review: weekly, as outlined above. This clinical lab results will be scanned in the electronic health record and except for CRP, results will be reported to participants.

Research blood work	Participants	• At Hursting lab • HPDP	no	Samples will be stored at Hursting Lab until all are collected. Results will be entered into Excel spreadsheet and sent to HPDP.
DNA analysis	Participants	--	no	Blood for DNA analysis will be stored de-identified as part of this study for possible future analysis. Samples will be stored at Hursting Lab.
Process data collected use Web-based counseling program.	Participants	• Sheps server • HPDP	yes	Data collected by web-based counseling program. These data will reside on the Sheps Center server until downloaded into a Excel file and sent to HPDP.
Data sets for analysis	Participants	• REDCap • HPDP • CSCC	yes and no	Analysis datasets created from REDCap datasets. Will be stored on Study's Microsoft Team's account. These dataset will have identifiers. De-identified REDCap data sets and other study datasets will be sent to CSCC for analysis.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in Section 6.2.1, Interventionist Training and Tracking.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern according to the guidelines of the UNC IRB. Protocol deviations will be reported to the UNC IRB as specified by the IRB guidelines, as outlined below:

- Will the IRB still review study deviations? Yes. Study deviations will be reviewed as part of post-approval monitoring by the IRB and/or the Clinical Trials Quality Assurance (CTQA) program. The IRB may also request your deviations records during its review of NSI. With this change, you will need to provide study deviation records at the request of the IRB.
- How will I provide the deviation to the IRB for review? At the request of the IRB, you may provide the deviation log to the IRB outside of IRBIS. The procedure for providing the deviation log will be outlined at the time of the request.
- Why are the changes being made? This new process is a way to meet regulatory requirements, focus resources on review of deviations involving increased risks to subjects, and reduce burden on IRB reviewers and investigators.
- Do I need to do anything? Aside from no longer providing deviation summaries at continuing review, you should be tracking study deviations as before. If you do not already have a deviation log for the study, we highly recommend you begin using the deviation log template provided

here: *https://research.unc.edu/files/2018/06/ProtocolDeviation-Tracking-Log.docx*. If you choose to use a different form, be sure that the one you use includes all the same elements as found in the template. It is even more important now to familiarize yourself with SOP 1401, as failure to promptly report new safety information (NSI) could be considered serious or continuing noncompliance.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The data issues to be described in this section are covered in Section 10.1.8.

10.1.9.2 STUDY RECORDS RETENTION

Study data will be maintained for at least 10 years after final data collection.

10.1.10 PROTOCOL DEVIATIONS

This study will follow the protocol deviation guidelines from the UNC IRB, as outlined below:

Purpose:	To record all protocol deviations that occur at a study site for both observational and interventional clinical research studies. IMPORTANT: This log is maintained in the Study Binder (Synonyms for this binder include Investigator Binder, Regulatory Binder, Investigator Site File [ISF], and Study File.) and should be made available upon request for review by the IRB and the Sponsor's monitor. Deviations should be reported to the IRB of record as per the IRB Standard Operating Procedures. See OHRE/IRB SOP 1401 for reporting requirements for deviations to the UNC IRB.
Audience/User:	Study coordinators, principal investigators (PIs), other site staff, clinical monitor

Best Practice Recommendations:

- Record protocol deviations in the tracking log as they occur, to ensure completeness and accuracy of the data.
- The site PI should sign each form after it has been completed or immediately prior to a monitoring visit. If it has been signed with fewer than five deviations entered into it, the next identified deviation should be reported on a new page to ensure that all deviations have been reviewed by the PI.
- Number each page and identify the final page of the log by indicating FINAL in the page number field.
- Store pages in reverse chronological order, with the newest pages of the log placed at the front of the section.
- Remove this page before using the log.

***DEVIATION CATEGORIES:**

A. Informed Consent
B. Eligibility
C. Protocol implementation
D. Reporting
E. Other, specify in log

**DEVIATION CODES: Numbers listed by the sample protocol deviations

Informed Consent (Category A)

1. Failure to obtain informed consent
2. Consent form used was not current IRB-approved version
3. Consent form does not include updates or information required by IRB
4. Consent form missing

5. Consent form not signed and dated by participant
6. Consent form does not contain all required signatures
7. Other, specify in log

Eligibility (Category B)

8. Participant did not meet eligibility criterion
9. Randomization of an ineligible participant
10. Participant randomized prior to completing Baseline Assessment, etc.
11. Randomization and/or treatment of participant prior to IRB approval of protocol
12. Other, specify in log

Protocol implementation (Category C)

13. Failure to keep IRB approval up to date
14. Participant receives wrong treatment
15. Participant seen outside visit window
16. Use of unallowable concomitant treatments
17. Prescribed dosing outside protocol guidelines
18. Missed assessment
19. Laboratory tests not done
20. Missed visit
21. Other, specify in log

Reporting (Category D)

22. Not submitting reportable information to the IRB within 7 days
23. Failure to respond to the NSI stipulations in the requested timeframe
24. Other, specify in log

Other (Category E)

25. Other, specify in log

IRB Study #		**Site Name/Number:**	
Protocol Title (Abbreviated):		**Protocol ID/Number:**	

Principal Investigator:					Page number [1]:				
Ref No.	**Subject ID**	**Date of Deviation**	**Date Identified**	**Deviation Description**	**Dev. Type [2]**	**Resulted in AE?**	**Did Subject Continue in Study?**	**Meets IRB Reporting Req. (I.e. NSI) (Yes/No)**	**IRB Reporting Date**
1									
2									
3									
4									
5									
6									
7									

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting the principle investigators. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial according to the guidelines set forth by the Conflict of Interest Program at UNC.

10.2 ADDITIONAL CONSIDERATIONS

N/A.

10.3 ABBREVIATIONS AND SPECIAL TERMS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list). Special terms are those terms used in a specific way in the protocol. For instance, if the protocol has therapist-participants and patient-participants, those terms could be included here for purposes of consistency and specificity.

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality

CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Version	Date	Description of Change	Brief Rationale
1.0	2/12/20	Initial Protocol Document	This serves as the current protocol approximately 6 weeks before first participant is enrolled. We anticipate an updated Version 1.1 to be submitted before enrollment of the first participant.
1.1	2/26/20	Step 5, Section 5.5 updated	Step 5 updated to allow enrollment goal of 40% for sub-groups with fewer potential participants available for enrollment
1.2	2/28/20	Stool protocol added	To asses change in stool microbiome in response to the interventions. **This protocol was submitted to the UNC IRB on 3/2/20 and approved on 3/12/10.**
1.3	2/22/21	Update protocol for Wave 2 recruitment	Wave 2 practices are smaller so will use cycle size of 60.
1.4	3/4/21	Protocol for physician review of EHR added	Protocol update.
1.5.	3/25/21	Sec 8.1.3a. Protocol amended to include time intervals for study activities after hospitalization: Sec 8.1.3a	Self-explanatory
1.6	3/25/21	Sec. 8.1.3.3 a. Phlebotomy protocol update intervals for collection study samples after randomization visit and collection of specimens at UNC labs.	Self-explanatory
1.7	7/25/21	Sec. 8.2. Decision made to send Epic staff message to PCP for LDL > 190 and not otherwise addressed in the medical record.	Self-explanatory
1.8	11/4/21	Sec 5.2. HIV controlled defined as undetectable RNA and CD4 count above 400.	Self-explanatory
1.9	6/8/25	Entire protocol reviewed with minor edits to confer changes to protocol.	Self-explanatory

		Last IRB approved change to protocol was 5/11/23.	

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