CLINICAL STUDY PROTOCOL

Title	**FEASIBILITY OF THE "PASO A PASO" WEIGHT LOSS PROGRAM FOR MEXICAN & CENTRAL AMERICAN PATIENTS WITH METABOLIC-DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)**
Sponsor	**NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES**
Baylor College of Medicine No	**H-55723**
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1. INTRODUCTION

1.1 STUDY RATIONALE

Metabolic-dysfunction associated steatotic liver disease (MASLD) is a highly prevalent public health problem that disproportionately hurts Mexican and Central Americans (M/CA). Weight loss through behavioral changes in diet and physical activity can lead to reductions in liver fat, injury, and fibrosis, but is rarely successfully achieved. Tailored behavioral weight loss interventions may improve the outcomes of M/CA patients with MASLD. This study's overarching purpose is to assess the feasibility of a weight loss program called "Paso a Paso: Rumbo a Un Higado Sano" among M/CA adult patients with MASLD.

1.2 BACKGROUND

Metabolic dysfunction associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease in the U.S. MASLD is characterized by an accumulation of liver fat consequent to excessive body fat and the metabolic syndrome. People of Mexican and Central American heritage (M/CA), bear the highest burden of disease compared to NHW, Blacks, and other Hispanic subgroups.

MASLD can progress from quiescent liver fat to necroinflammatory fat (steatohepatitis) with progressive fibrosis to cirrhosis. Patients with severe fibrosis (stage F2-4 on liver biopsy) have the highest risk of liver related complications and mortality. Age, sex, specific genetic variants, type 2 diabetes, adiposity, and specific health behaviors (unhealthy diets, physical inactivity) are risk factors for severe fibrosis in MASLD. Of these, health behaviors are the only modifiable factors associated with MASLD improvement.

Behavioral change is the cornerstone of MASLD treatment. The American Association for the Study of Liver Disease, American College of Gastroenterology, and American Gastroenterology Association recommend weight loss via behavioral change as the first line treatment for MASLD. Weight loss of 5-10% through sustained lifestyle modifications improves hepatic fat, steatohepatitis, and fibrosis. Dietary change (reductions in total calories and simple sugar intake) and increased aerobic physical activity are also associated with improvements in liver fat and insulin resistance, independent of weight loss.

The data show that patients with MASLD do not lose weight under standard Hepatology care. In a systematic review of 24 papers worldwide, we found that patients with MASLD and engaged in routine hepatology care, gain an average of 1% weight (rather than lose weight) over 1 year. Locally, in a single center, study of 322 patients with MASLD (90% M/CA) followed over 16 months, we found that 84% did not lose weight despite receiving the current standard of care ("usual care"), which is to promote weight loss behaviors through brief clinician and dietitian led discussions. These data highlight the need for interventions that lead to sustainable weight loss in MASLD.

In qualitative research, we have found that M/CA patients struggle with several barriers to making weight loss behavioral changes. Many of the behavioral change barriers are longstanding, predating their MASLD diagnosis. Patients express feeling alone, unsupported, and confused in their weight loss journey. They articulate a need for more structured behavioral support from medical providers (Baylor College of Medicine IRB Protocol #H-49779, unpublished data).

For all these reasons, there is a clear need for structured behavioral weight loss interventions tailored for M/CA patients with MASLD. To address this need, we adapted an existing evidence-based weight loss intervention called the "Look AHEAD Lifestyle Program" for the clinical, social, and cultural needs of M/CA patients with MASLD using intervention mapping and focus group methodology (BRAIN IRB

protocol # H-51086). The adapted intervention is called "Paso a Paso: Rumbo a Un Higado Sano" (Step by Step: Journey to a Healthy Liver." The intervention consists of a series of 16 one-hour long weekly to biweekly group counseling sessions delivered over 6 months. This protocol outlines a single arm study to test the feasibility of the intervention among 50 M/CA patients with MASLD.

1.3 RISK - BENEFIT ASSESSMENT

Behavioral weight loss programs build on an extensive amount of data generated in the context of obesity, metabolic syndrome, type 2 diabetes, and MASLD. In the context of these related conditions, behavioral weight loss programs have been found to be safe and well tolerated.

The main benefits and risks are described in the sections below.

1.3.1 RISKS

The risks expected as part of participation in this trial are minimal and outlined here.

Intervention related risks
The intervention is the Paso a Paso Program (weight loss program) that consists of group sessions during which participants are given counseling for dietary modification and increased physical activity. These are the potential risks: 1) Participants who have type 2 diabetes are at risk for hypoglycemia during the intervention due to reductions in caloric intake and if they lose weight. To mitigate this risk, the health educator (overseen by the PI) will discuss risk, signs, and management of hypoglycemia with each diabetic participant. With the PI, the health educator will review diabetic participants' blood sugars prior to intervention start and weekly through the intervention. The PI will advise patients of necessary diabetes medications changes accordingly. She will do this in conjunction with participants' primary diabetes providers. 2) With initiation of or increases in physical activity, there is the risk of injury. To mitigate this risk, the program teaches participants safety measures to follow and warning signs to monitor as they increase their physical activity levels. 3) With dietary modifications, there's the risk of discomfort (feeling hungry, increased abdominal bloating). As part of the program, participants are counseled to anticipate this discomfort and how to manage it.

Study Procedure related risks
The study procedures involve questionnaires, muscle strength and body weight measurement, and transient elastography of the liver. It also involves the optional procedures of one-on-one interview and a research blood sample. These are the potential risks: 1) Questionnaire and interview are associated with potential loss of time, inconvenience, emotional distress. 2) Transient elastography is a form of ultrasound obtained using a probe placed on the abdomen. Aside from mild pressure that is applied on the abdomen to obtain measurements of the liver, it is not associated with any specific risks 3) Optional study blood sample: This involves venipuncture and the main risks are related discomfort and transient bruising.

1.3.2 BENEFITS

Patients who participate in this study may directly benefit by losing weight, which is associated with improvement in MASLD. They may also gain greater knowledge about their liver disease and healthy eating and physical activity habits. Family members who participate in this study may directly benefit by learning more about participants' liver disease and weight loss.

1.3.3 RISK VERSUS BENEFIT SUMMARY

This project will help to improve MASLD among Mexican and Central American patients by investigating the feasibility of a useful weight loss intervention and generating evidence to guide interventions among this population.

The potential benefits for individual participants, family members, and society are much greater than any risk. For individual participants, the potential benefit is weight loss. Weight loss can reverse MASLD related liver injury and slow down progression to cirrhosis. Changes in diet and physical activity (which are promoted by this trial's weight loss program) and weight loss can also improve the metabolic comorbidities (diabetes, hypertension, dyslipidemia) that accompany MASLD. Thus, the benefits of participating in this study outweigh the risks of potential hypoglycemia (risk of which will be mitigated through measures described and monitored closely), mild discomfort associated with study procedures. For society, the potential benefit is greater information about how to intervene for weight loss among the target population, which is high risk for progressing to MASLD cirrhosis.

2. STUDY DESIGN

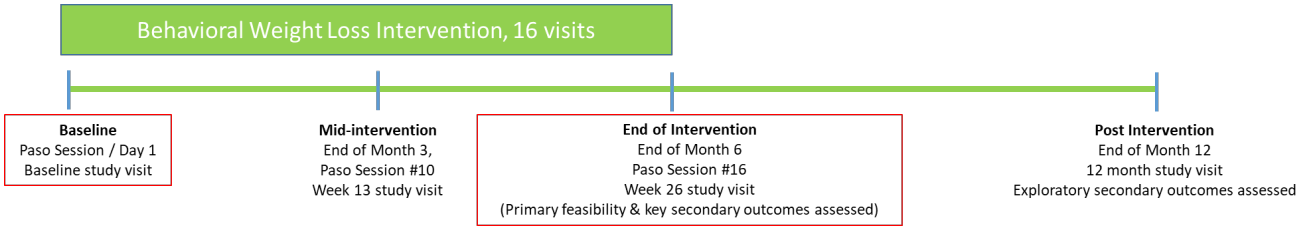
2.1 STUDY DESIGN - OVERVIEW

This is a 1 year single arm clinical trial evaluating the feasibility of the "Paso a Paso" weight loss program for Mexican & Central American patients with metabolic-dysfunction associated steatotic liver disease (MASLD). The main trial design is shown in Figure 1.

Two sub-studies are embedded into the main study.

1. Qualitative Sub-Study of Intervention and Trial Feasibility & Acceptability
   A qualitative assessment of intervention and trial feasibility and acceptability will be conducted among four subsets of participants: 1) patients who decline study participation, 2) Main study participants whodrop out of the study, 3) Main study participants who complete the study but attend 8 or fewer intervention sessions, and 4) Main study participants who complete the study with attendance of more than 8 intervention sessions.

2. Family/Friend Sub-Study
   An sub-study will be conducted among people that main study participants identify as influential on their eating and exercise habits to determine the effect of the intervention on social support.



2.2 STUDY DESIGN - RATIONALE

It is important to pilot test an intervention to determine whether and how to refine it to optimize feasibility and acceptability prior to moving forward with large scale efficacy testing. This trial is designed to address that primary objective. Therefore, we have elected to pilot test the Paso Program's among 50 participants using a single arm trial design. We elected a single arm trial design (quasi-experimental design), instead of a randomized control trial, because the focus is on the intervention's feasibility (rather than its efficacy). Secondary objectives will be to determine changes physiologic, behavioral, and behavioral determinant endpoints over 6 months and 1 year. Also, we will compare change in weight with an observational group of 50 patients who receive usual care to obtain preliminary weight loss efficacy data for future larger-scale efficacy testing.

2.3 HYPOTHESIS

The Paso Feasibility study's primary hypothesis is that the intervention is feasible, defined as average session attendance study participants over the 6 month program. The primary outcome measure will be average session attendance >8 across study participants. The study is powered (80%) to detect that the average number of classes attended will be greater than 8 with 50 participants. The scientific premise of the primary hypothesis is based on Centers for Disease Control Diabetes Prevention Program (CDC-DPP) recognition criteria that defines program completion as attendance of ≥9 sessions in months 1-6. An evaluation of the DPP over 2015-2018 found that compared with participants who attended <9 sessions, those who attended ≥9 sessions in the first 6 months were 1.8 to 2.2 times more likely to achieve ≥ 5% weight loss from baseline.

2.4 OBJECTIVES

Primary objective:

- To evaluate the intervention's feasibility, defined as session attendance.

Secondary objectives:

- The key secondary objective is to compare average percent change in weight at the end of 6 months among M/CA enrolled in the intervention (as part of this study) with a parallel observation cohort of M/CA patients who received routine Hepatology care (derived from BRAIN IRB protocol # H-36814).

- Additional secondary objectives are to assess changes among participants in the following at the end of the 6 intervention (items marked with * are also assessed at 6 month end-of-intervention/1 year study follow-up):
    a. Total body weight*
    b. Muscle strength (hand grip dynomometry)*
    c. Fibroscan measured continued attenuation parameter*
    d. Fibroscan measured liver stiffness measurement*
    e. Liver enzymes*
    f. Metabolic syndrome features (triglycerides, HDL, hemoglobin a1c, HOMA-IR)*
    g. Average daily calorie consumption*
    h. Average daily fat intake*
    i. Dietary quality*

j. Average daily steps
k. Average time spent doing moderate to vigorous physical activity every week*
l. Quality of life
m. Average alcohol intake*
n. Perceived stress
o. Perception of MASLD
p. Perception of weight loss and behavioral change efficacy for MASLD treatment
q. Social support for exercise*
r. Social support for diet*

Exploratory objectives:

- Additionally exploratory objectives are to assess changes among participants in the following at the end of 1 year
    a. Total body weight*
    b. Muscle strength (hand grip dynomometry)*
    c. Fibroscan measured continued attenuation parameter*
    d. Fibroscan measured liver stiffness measurement*
    e. Liver enzymes*
    f. Metabolic syndrome features (triglycerides, HDL, hemoglobin a1c, HOMA-IR)*
    g. Average alcohol intake*
    h. Average time spent doing moderate to vigorous physical activity every week*
    i. Social support for exercise*
    j. Social support for diet*

Exploratory qualitative objectives:

- To examine factors that influence behavioral intervention and clinical trial participation, feasibility, and acceptability among patients, including barriers, facilitators, and areas for improvement.

Exploratory objectives among family members:

- To assess changes in the following among family members of intervention recipients over 6 months:
    - Perception of MASLD
    - Perceived effect of weight loss, diet, and physical activity on MASLD
    - Social support for weight loss and behavioral change

2.5 ENDPOINTS

Name	Time of endpoint assessment	Description
Primary endpoint among study participants		
Feasibility	6 months	Average attendance > 8 sessions
Key Secondary endpoint among participants		
Change in % weight	6 months	average % change in weight
Secondary outcomes among participants		
Change in absolute weight*	6 months	Average absolute weight change (kg)
Change in muscle strength*	6 months	Average change, measured by hand grip dynamometry

Change in liver stiffness values assessed by transient elastography*	6 months	Average change
Change in continued attenuation parameter assessed by transient elastography*	6 months	Average change
Change in ALT*	6 months	Average change
Change in AST*	6 months	Average change
Change in triglycerides*	6 months	Average change
Change in HDL*	6 months	Average change
Change in LDL*	6 months	Average change
Change in hemoglobin A1C*	6 months	Average change
Change in diet quality*	6 months	Average change in Health Eating Index, diet history questionnaire
Change in average daily calorie intake	6 months	Average change (calories), diet history questionnaire
Change in average fat intake	6 months	Average change (grams), diet history questionnaire
Change in alcohol intake*	6 months	Average change (drinks), AUDIT-C
Change in average time spent doing moderate to vigorous physical activity every week	6 months	Average change (accelometer)
Change in average time spent doing moderate to vigorous physical activity every week	6 months	Average change, IPAQ score
Change in average daily steps	6 months	Average change (accelometer)
Change in quality of life	6 months	Average change, score (PROMIS)
Change in perception of MASLD	6 months	Change in average composite score, Illness perception questionnaire
Change in perceived treatment efficacy	6 months	Change in average composite score, treatment efficacy questionnaire
Change in dietary self-efficacy*	6 months	Average change, score
Change in physical activity self-efficacy*	6 months	Average change, score
Change in social support for diet*	6 months	Average change, score
Change in social support for exercise*	6 months	Average change, score
Change in perceived stress	6 months	Average change, score
Change in weight*	1 year	Average absolute weight change (kg)
Change in muscle strength*	1 year	Average change, measured by hand grip dynamometry
Change in liver stiffness values assessed by transient elastography*	1 year	Average change
Change in continued attenuation parameter assessed by transient elastography*	1 year	Average change
Change in ALT*	1 year	Average change
Change in AST*	1 year	Average change
Change in triglycerides*	1 year	Average change
Change in HDL*	1 year	Average change
Change in LDL*	1 year	Average change
Change in hemoglobin A1C*	1 year	Average change
Change in diet quality*	1 year	Average change, score
Change in alcohol intake*	1 year	Average change (drinks), AUDIT-C

Change in average time spent doing moderate to vigorous physical activity every week	1 year	Average change, IPAQ score
Change in dietary self-efficacy*	1 year	Average change, score
Change in physical activity self-efficacy*	1 year	Average change, score
Change in social support for diet*	1 year	Average change, score
Change in social support for exercise*	1 year	Average change, score
Exploratory qualitative endpoint among participants		
Barriers, facilitators, and ways to improve participation, feasibility, and acceptability of intervention and trial		
Exploratory endpoints among family members		
Change in perception of MASLD among family members	6 months	
Change in perceived treatment efficacy of weight loss and behavior change on MASLD among family members	6 months	

3. STUDY POPULATION

3.1 MAIN STUDY POPULATION ELIGIBILITY CRITERIA

Sample Size = 50

Eligibility

Adult patients (between 18 and 65 years of age) who self-report Mexican or Central-American ethnicity, have a documented diagnosis of MASLD, and body mass index ≥25kg/m2 are eligible for the main study.

Inclusion criteria

For an eligible participant, all inclusion criteria must be "yes" at time of consent

1. Diagnosed with MASLD (defined per guideline based diagnostic criteria: evidence of steatosis with at least 1 metabolic syndrome feature)
2. Self-reported Mexican or Central American ethnicity
3. Age between 18 and 70 years
4. BMI≥25kg/m^2
5. Able to read and write English and/or Spanish

Exclusion criteria

For an eligible participant, all exclusion criteria must be "no" at start of intervention (**Paso program day 1**):

1. ≥5% weight loss over the prior 3 months
2. HbA1c ≥9.0% within 30 days of weight loss program initiation*
3. History of bariatric surgery
4. Advanced liver disease, defined as:

platelet count < 150,000,
serum albumin <3.5 g/dL, except as explained by non-hepatic causes.
INR >1.4 unless due to therapeutic anticoagulants or laboratory error.
Total bilirubin ≥2 mg/dL (unless explained by Gilbert Syndrome).
Presence of esophageal varices,

5. Any history of liver disease decompensations** or hepatocellular carcinoma,
6. History of any organ transplant (including liver transplant)
7. Active HCV infection (defined as HCV Ab positive with detectable viral load)*, Hepatitis B infection (defined as positive HBsAg) and/or other etiologies of chronic liver disease (AIH, PBC, Wilson disease, PSC) or acute hepatic injury.
8. Ongoing heavy alcohol use defined as 320-420grams/week
9. SGLT2 inhibitor or Glucagon-like peptide 1 (GLP-1) agonist therapy for diabetes treatment (e.g., exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide, and albiglutide) or for weight loss (e.g., semaglutide at doses up to 2.4 mg subcutaneous weekly) must be at a stable dose for at least 6 months prior to study entry with stable weight (defined as <5% weight loss in the 12 weeks prior to study entry)*
10. Pioglitazone is allowed if on a stable dose for 3 months prior to study entry
11. current pregnancy/nursing or planned pregnancy
12. conditions limiting dietary calorie reduction or physical activity
13. Active cancer, defined as cancer requiring treatment in the past five years, except for non-melanoma skin cancers or cancers that have clearly been cured, stable and being monitored by primary doctor or oncologist without active treatment, or carries an excellent prognosis (e.g., Stage 1 cervical cancer)
14. unstable cardiac disease
15. intestinal resection or malabsorption disorders
16. life expectancy<2 years
17. competing serious medical or psychiatric comorbidity
18. HIV infection
19. History of noncompliance (>3 primary care, endocrine, and/or hepatology clinic no-shows in the past year)

Notes

*Allowed into the trial are patients who:

- On a stable dose of GLP1 agonist or SGLT2 inhibitor ≥ 6months prior to paso weight loss program day 1 with stable weight (defined as <5% weight loss) for 3 months.
- History of treated or spontaneously cleared HCV infection 1 year prior to study entry (defined as HCV Ab + with negative viral load)
- If screening HbA1c was ≥9.0% and a new anti-diabetic therapy was initiated, patient may be allowed into the trial if repeat HbA1c falls below exclusionary cutoff 30 days prior to paso weight loss program day 1.

**Decompensations are defined as any history of:

- Gastroesophageal variceal bleeding
- Ascites due to cirrhosis
- Concern for subclinical or overt hepatic encephalopathy, lactulose treatment, or other treatment for hepatic encephalopathy.

3.2 QUALITATIVE SUB-STUDY POPULATION

The qualitative substudy will be conducted among 4 types of participant groups, outlined below. The main study decliners represent the only type of participants who are not enrolled in the main study. All other types of participants are main study participants.

3.2.1 MAIN STUDY DECLINERS:

- Sample size: 5-10
- Inclusion criteria - People who qualify for the main study but decline main study participation.
- Exclusion criteria - none

3.2.2 MAIN STUDY DROP OUTS:

- Sample size: 5-10
- Inclusion criteria – Main study participants who have consented and enrolled into the main study but drop out/early terminate the study.
- Exclusion criteria – none.

3.2.3 MAIN STUDY COMPLETERS WITH <=8 SESSIONS ATTENDED:

- Sample size = 5-10
- Inclusion criteria – Main study participants who complete the study but attend fewer than 8 intervention sessions.
- Exclusion criteria – none

3.2.4 MAIN STUDY COMPLETERS WITH >8 SESSIONS ATTENDED:

- Sample size = 5-10
- Inclusion criteria – Main study participants who complete the study and attended 8 or more intervention sessions.
- Exclusion criteria - none.

3.3 FAMILY/FRIENDS SUB-STUDY POPULATION

This substudy includes family or friends that study participants identify as potentially influential on their eating and exercise habits.

Inclusion Criteria

1. Identified family/household member or friends of main study participant
    a. Family refers to only those living in the same household.
    b. Friends refers to any friend or family member not living in the same household.
2. Age >18 years
3. Able to speak English or Spanish
4. Willing to participate in study assessments and provide verbal informed consent

Exclusion Criteria - none

4. STUDY INTERVENTION – PASO A PASO PROGRAM

4.1 PASO-A-PASO PROGRAM OVERVIEW

All enrolled patients will receive the intervention. The intervention that will be implement is an adapted version of the Look AHEAD Lifestyle Program, which was an NIH developed weight loss intervention. This intervention was adapted (BRAIN IRB protocol # H-51086) utilizing principles of intervention mapping and use of focus group discussions with expert stakeholders (i.e. dietitians, physical therapists, physicians) and patients. The intervention consists of a series of 16 one-hour-long group counseling sessions scheduled every 1-2 weeks over 26 weeks. The session are semi-structured classes and led by a health educator. Each session covers a specific topic on eating, physical activity, or behavioral strategies to make and maintain behavioral changes. Each session has a curriculum with a counselor's guide and patient facing materials. Teaching methods include discussions, practice activities, demonstrations. The intervention will be delivered in-person and virtually. English and Spanish sessions will be offered separately. This hybrid delivery format is offered because of patient preference expressed as part of the focus groups conducted by our team.

4.2 PASO-A-PASO SESSION OUTLINE & OBJECTIVES

Week	**Weight Loss Program Session**
1	1. Welcome
2	2. The calorie balance
3	3. Ways to eat fewer calories
4	4. Let's do more physical activity
5	5. Control your environment
6	6. Problem Solving
7	7. Physical activity, a lifestyle
9	8. Healthy Eating
11	9. Cook Healthy
13	11 Respond to negative thoughts
15	12 You took a missed step, now what?
17	13. Emotions and You
19	15. make social cues work for you
21	16. you can manage stress
24	17. Don't lose your motivation
26	18. See you later and good luck!
Given to participants to read on their own	10. Eat healthy away from home
Given to participants to read on their own	14. prevent boredom by incorporating something new

Session 1. Welcome to the program!
For this session we will review the following objectives:

- We will teach you the principles of healthy eating and exercise.

- We will teach you strategies to integrate these principles into your lifestyle.
- You will learn these strategies in our group classes over the next 26 weeks

Session 2. Balancing calories
For this session we will review the following objectives:
- The calorie balance
- How to move your calorie scale to lose weight
- How the type and amount of food you eat affect your calorie balance

Session 3. Ways to eat fewer calories
For this session we will review the following objectives:
- Two ways to eat fewer calories and less fat: weigh and measure the food you eat
- How to follow the program's eating plan
- How to keep track of everything you eat and drink

Session 4. Let's do more physical activity!
For this session we will review the following objectives:
- Doing more cardiovascular exercise- We will talk about it in this session
- Moving more in your day-to-day- We will talk about it in a future session
- Strengthening your muscles- We will talk about it in a future session
- Today we will focus on cardiovascular exercise.

Session 5. Control your environment
For this session we will review the following objectives:
- What is a stimulus and how does it cause unhealthy eating and physical activity habits?
- Common Stimuli of Unhealthy Habits
- Ways to change unhealthy habits associated with these triggers
- How to make an action plan to identify and change the stimuli that influence your eating and physical activity habits

Session 6. Problem solving
For this session we will review the following objectives:
- Many things can get in the way when we want to be physically active and eat a healthy diet. If you take a wrong step, you can still get back on track.
- In this session we will present you with a troubleshooting guide. This will help you understand what happened and how to prevent another misstep in the future so you can achieve your goals.

Session 7. Physical activity: a lifestyle
For this session we will review the following objectives:
- Increase the movement you do in your daily life- We will talk about it in this session
- Doing more cardiovascular exercise- We talked about it in session 4.
- Strengthening your muscles- We will talk about it in a future session.
- Today we will focus on increasing your daily movement.

Session 8. Eat healthy
For this session we will review the following objectives:
- How to eat

- What does he eat
- The balanced plate and how to use it as a guide to eating healthy
- The different types of micronutrients: carbohydrates, proteins and fat

Session 9. Cook healthy
For this session we will review the following objectives:
- Substitute ingredients to create meals with fewer calories and less fat s
- Different methods of cooking food
- Find healthy recipes (with online resources)
- The truth about diets and popular food trends

Session 11. Respond to negative thoughts
For this session we will review the following objectives:
- How negative thoughts affect our eating and physical activity habits
- Common types of negative thoughts
- How to respond to negative thoughts

Session 12. You took a missed step... Now what?
For this session we will review the following objectives:
- Maintain a positive outlook
- Follow the 5 steps to solve problems

Session 13. Emotions and you
For this session we will review the following objectives:
- How stress and emotions influence your eating and physical activity habits
- How to control stress

Session 15. Make the social cues work in your favor
For this session we will review the following objectives:
- How social cues (what other people say or do) affect your diet and physical activity
- The transition from following our eating program to following your own eating plan

Session 16. You can manage stress
For this session we will review the following objectives:
- How stress affects health
- How to prevent stress
- How to control stress

Session 17. DON'T lose your motivation
For this session we will review the following objectives:
- How far you've come since you started this program 6 months ago
- How to maintain the healthy habits you have developed
- How will you maintain

Session 18. See you later and good luck!
What you have learned:
- Eat healthy

- Live a physically active life
- Implement tools to make and maintain healthy habits

Optional session materials - offered to participants to review on their own:

Session 10. Eat healthy away from home
For this session we will review the following objectives:

- Factors affecting eating habits and food choices when eating away from home (in restaurants, takeaways, social events, friends'/other family's houses)
- Ways to create habits that support healthy eating while you're away from home
- Practice using the tips in this session

Session 14. Prevent boredom by incorporating something new!
For this session we will review the following objectives:

- Increase the movement you do in your daily life- We talked about it in a previous session.
- Doing more cardiovascular exercise- We talked about it in a previous session.
- Strengthening your muscles
- Today we will focus on incorporating strengthening

5. STUDY ASSESSMENTS & PROCEDURES

5.1 MAIN STUDY ASSESSMENTS

5.1.1. TIMELINE OF STUDY ASSESSMENTS

v4		Intervention									Follow-Up	
	Window for baseline assessments	Baseline		Session 2	Session 3/4/5/6/7/8/9	Mid-Intervention	Window for mid-intervention assessments	Session 11/12/13/14/15	End of Intervention	Window for end-intervention assessments	Post-Intervention	Window for post-intervention assessments
		Consent	Day 1 Session 1			Session 10			Session 16		6 month FU	
		In-Person or Virtual	In-Person	In-Person	In-Person or Virtual	In-Person		In-Person or Virtual	In-Person			
Timing of Visits (Weeks)		0	1	2	3/4/5/6/7/9/11	13		15/17/19/21/24	26		52	
Visit Windows (Days)		-90 / +7		0	0	0		0	-7 / +30		-30 / +30	
Obtain Informed Consent		X										
Confirmation of Eligiblity		X										
Medical History		X										
Medications		X				X			X		X	
Session Attendance			X	X	X	X		X	X			
Weight			X			X			X		X	
Height			X									
Muscle Strength[A]			X			X			X		X	
Physical Activity Assessment by Accelometer (Actigraph)	wear actigraph anytime from -14 to +7 of day 1 (most practical from program day 1 (session 1) to day 7 (session 2))		D1-D7						X	(-7 days to + 7 days of session 16)		
Questionnaires		X[D1]	X[D2]			X[D3]			X[D4]		X[D5]	
Demographics	as early as day of consent to program day 1	x										
Acculturation	as early as day of consent to program day 1	x										
Stages of change questionnaire	as early as day of consent to program day 1	x										
Health literacy screen	as early as day of consent to program day 1	x										
Food insecurity	as early as day of consent to program day 1	x										
AUDIT-C	as early as day of consent to program day 1	x							X	(-7 days to + 7 days of session 16)	x	**(-1month to 1month of time point)**
Smoking	as early as day of consent to program day 1	x										
Quality of Life	(-4 weeks to program day 1)	x							X	(-7 days to + 7 days of session 16)		
PHQ9 (depression)	as early as day of consent to program day 1	x										

BEDS (binge eating)	as early as day of consent to program day 1	x							X			
Perceived Stress	as early as day of consent to program day 1	x							X	(-7 days to + 7 days of session 16)		
Self-efficacy	(-4 weeks to program day 1)	x				x	(-7 days to + 7 days of session 10)		X	(-7 days to + 7 days of session 16)	x	**(-1month to 1month of time point)**
Social Support	(-4 weeks to program day 1)	x							X	(-7 days to + 7 days of session 16)		
Disease knowledge/perception seriousness	(-4 weeks to program day 1)	x							X	(-7 days to + 7 days of session 16)		
Outcome Expectation	(-4 weeks to program day 1)	x							X	(-7 days to + 7 days of session 16)		
IPAQ (researcher administered*)	(-14 days to +7 days of program day 1)	x							X	(-7 days to + 7 days of session 16)		
RAPA	(-14 days to +7 days of program day 1)	x							X	(-7 days to + 7 days of session 16)	x	**(-1month to 1month of time point)**
DHQ3 (researcher administered*)	(-4 weeks to +7 days of program day 1)	x							X	(-7 days to + 7 days of session 16)		
Clinical Laboratory Assessments		X	X						X	(-7days to +1 month of session 16)	X	**(-1month to 1month of time point)**
Basic metabolic panel	(-180 days to program day 1)											
Liver enzymes (AST, ALT, Tbilirubin, albumin, protein)	(-90 days tof program day 1)											
Hemoglobin a1c	(-90 days tof program day 1)											
Complete blood count	(-180 days to program day 1)											
lipids	(-180 days to program day 1)											
PT, INR	any available											
Liver etiology workup	any available											
Hepatitis/HIV	any available											
Immunology	any available											
Actin smooth muscle	any available											
Fibroscan[E]	(-6 months of program day 1)	X	X[E1]						X	(-7days to +1 month of session 16)	X	**(-1month to 1month of time point)**
Exploratory inflammatory & fibrosis serological markers[F]	(-3 months of program day 1)	X	X[F1]						X	(-7days to +1 month of session 16)		

Main study procedures and assessments will be performed at four study time points (baseline, mid-intervention, end of intervention, and post intervention) as outlined in the SoA.

Baseline Study Assessments

These assessments will be completed in a window ranging from 6 months before to 7 days after program day 1. See flowsheet for exact timeline. The assessments do not have to be done during a single research visit.

1. Questionnaires
2. Body weight
3. Muscle strength
4. Transient elastography of the liver
5. Abstract clinical data
6. Actigraphy
7. Research blood sample (optional procedure)

Mid-Intervention Assessments: These assessment will be completed after 3 months of the intervention.

1. Questionnaire
2. Body weight
3. Muscle strength
4. Abstract diet and pedometer data from logs

End of Intervention Assessments / Early Termination Assessments

These assessments will be completed after intervention completion or at early termination (if a participant drops out early). The assessments do not have to be done during a single research visit.

1. Questionnaires
2. Body Weight
3. Muscle strength
4. Transient elastography of the liver
5. Actigraphy
6. Abstract clinical data
7. Abstract diet and pedometer data from logs
8. Research blood samples (optional procedure)

Post-Intervention Assessments

These assessments will be completed 6 months after intervention completion. The assessments do not have to be done during a single research visit.

1. Questionnaires
2. Body weight
3. Muscle strength
4. Transient elastography of the liver
5. Abstract clinical data

5.1.2 DESCRIPTION OF STUDY ASSESSMENTS

QUESTIONNAIRES

Questionnaires will be self-administered or research staff assisted, in-person, online, or by telephone, based on participant preference. Questionnaires will be completed at baseline, mid-intervention, end of intervention, and post intervention.

The following questionnaires will be collected as outlined in the SoA: demographic questionnaire, stages of change questionnaire in weight management, 3-Item health literacy, hunger vital sign, AUDIT-C, tobacco use questionnaire, PHQ-9, perceived stress scale, binge eating with BEDS-7, Dietary History Questionnaire III (DHQ III), International Physical Activity Questionnaire (IPAQ), Rapid Assessment of Physical Activity (RAPA), self-efficacy for diet and physical activity scales, Modified brief illness perception and perceived treatment efficacy questionnaires, and PROMIS global health.

DIET ASSESSMENT BY DHQ III

We will assess diet at baseline and end of intervention using the DHQ III. The DHQ will be administered with research staff assistance.

TRANSIENT ELASTOGRAPHY OF THE LIVER

FibroScan® measurements of liver stiffness and fat content will performed at the subject's baseline, mid-intervention, end of intervention, and post intervention visit, as outined in the SoA. Fibroscan is a form of ultrasound of the liver that measures continued attenuation parameter of the liver and liver stiffness.

FibroScan® should be performed under appropriate fasting conditions, which require a minimum of 3 hours without food or liquids, except for water. To ensure quality results, 10 measurements are required, with an interquartile range to median ratio (IQR/med) of less than 30%. When using SmartExam, the CAP score should be at 100%

The site must possess the necessary expertise in operating the FibroScan® device, and all operators are required to receive the necessary training. If SmartExam is available, it must be utilized for all examinations. If SmartExam is not available, the participant may still undergo scanning; however, the site must refrain from utilizing SmartExam for all subsequent exams throughout the duration of the trial. It is essential for sites to ensure that the probes are properly calibrated.

BODY COMPOSITION MEASUREMENTS

Body Weight

A portable scale will be employed to obtain weight measurements, and efforts will be made to use the same scale for all measurements to ensure consistency. The scale will be calibrated in accordance with the manufacturer's specifications. Weights should be recorded in kilograms, rounded to one decimal place.

Ensure that shoes are removed, and coats or jackets are taken off before taking measurements. Additionally, pockets should be emptied of all heavy objects, such as phones and keys, prior to weighing.

Height

The height measurement should be taken without footwear and recorded in centimeters.

Body Mass Index

The participant's body mass index (BMI) will be calculated by the electronic data capture system (REDCap), utilizing the height and weight recorded at the baseline visit.

Waist and Hip Circumference

Waist circumference is measured at the midpoint between the lower rib margin and the iliac crest. Hip circumference is measured around the widest part of the hips, typically around the top of the thighs and across the fullest part of the buttocks. Measures must be obtained in standing position with a non-stretchable measuring tape. The tape should be in contact with the skin without compressing the soft tissue. The subject should be instructed to breathe normally during the measurement. The same measuring tape must be used consistently throughout the trial. Circumference measurement should be recorded in centimeters.

MUSCLE STRENGTH ASSESSMENT BY HANDGRIP DYNOMETRY

A single operator will take all measurements for each subject in order to minimize interoperator variability. See relevant SOP for how to conduct procedure.

CLINICAL DATA ABSTRACTION

The following clinical data will be abstracted from participants' medical records: routine clinical laboratory testing, medical history, medications, and history of alcohol and drug use.

Clinical Labs

The following clinical laboratory assessment data will be abstracted from participants' medical records. Data from within the windows described in the SoA will be used for the following: hemoglobin A1C, liver enzymes, complete blood count, INR/PT, basic metabolic panel, lipids, hepatitis/HIV studies, immunology, and actin smooth muscle.

Medical History

The following medical history will be reviewed and recorded: diagnoses, progress notes, medications, lab or radiology findings, demographic information, and alcohol, drug and tobacco use.

Medications

The following medications will be recorded, as outlined in the SoA: diabetic, heart or blood pressure, cholesterol, non-alcoholic steatohepatitis (NASH), systemic glucocorticoids, estrogen, progestin, anabolic steroids, hormone replacement therapy or selective estrogen receptor modulators, and obesity or weight loss medications.

Alcohol and Drug Use

The following information related to alcohol use will be recorded: duration, ongoing use, quantity, alcohol misuse/dependence, treatment history. The following information related to drug use will be recorded: drug types, duration, ongoing use, frequency, dependence, treatment history.

PHYSICAL ACTIVITY ASSESSMENT BY ACCELOMETER

At baseline and end of intervention, participants will be asked to wear an accelometer for 7 days to measure physical activity.

PASO PROGRAM LOGBOOK DATA ABSTRACTION

Daily Calorie and Fat Intake

Participants will be asked to count their daily calorie intake and record this information in their 7-day logbook as part of the Paso program. Diet data will be abstracted from this 7-day log maintained by participants.

Pedometer Data

Participants will be asked to wear a pedometer and record their daily step count in their 7-day logbook issued. Pedometer data will be abstracted from the 7-day logbook maintained by participants.

RESEARCH BLOOD SAMPLES – OPTIONAL PROCEDURE

Research blood samples are being collected for exploratory inflammatory and fibrosis marker measurements.

Provision of research blood samples is an optional procedure. Participants who opt into this procedure will be asked to provide blood samples that will be stored in the population sciences repository for future inflammatory and fibrosis marker testing.

INTERVIEWS – OPTIONAL PROCEDURE

Participation in qualitative interviews is an optional procedure. Participants who opt into this procedure may be contacted at some point during the 26 week intervention to engage in a single interview.

We will interview three subtypes of main participants (see section 3.2). The single interview's objectives and guiding questions are designed to probe different aspects of program and study feasibility and acceptability across the three different types of main study participant. See section 5.2 for description of interviews.

All interviews will be conducted by telephone or in-person, according to the participant's preference. The interviews will be audio-recorded (if participant declines this, then notes taken), and transcribed and translated (either by 3rd party or internally be research staff based on participant preference). The interview data will be coded (with a non-identifiable study ID) and stored on the Baylor College of Medicine server.

5.1.3 INTERVENTION FIDELITY

We will assess Intervention fidelity using a checklist during each Paso session. A member of the research team will observe each session and complete the checklist. The session counselor and PI will both be blinded to the checklist finding until after the session is completed.

5.2 QUALITATIVE SUB-STUDY ASSESSMENTS

The embedded qualitative sub-study involves a single semi-structured interview. The interviews' objective and questions vary across each of the 4 qualitative sub-groups, as described below.

5.2.1 MAIN STUDY DECLINER

A single semi-structured interview is to be conducted at the time of declining study. The objective is to understand reasons for declining, barriers to participation, and suggestions to improve likelihood of participating in behavioral interventions and studies.

5.2.2 MAIN STUDY DROPOUT

A single semi-structured interview is to be conducted at the time of study dropout. The objective is to understand reasons for dropping out, barriers to participation, and suggestions to improve likelihood of adhering to behavioral interventions and studies.

5.2.3 MAIN STUDY COMPLETERS WITH <=8 SESSIONS ATTENDED:

A single semi-structured interview is to be conducted at the end of the 6 month intervention. The objective is to understand reasons for low attendance and suggestions to improve feasibility of the behavioral intervention and study participation.

5.2.4 MAIN STUDY COMPLETERS WITH >8 SESSIONS ATTENDED

A single semi-structured interview is to be conducted at the end of the 6 month intervention. The objective is to understand facilitators of high attendance, feedback, and suggestions to improve feasibility of the behavioral intervention and study participation.

5.3 FAMILY/FRIENDS SUB-STUDY ASSESSMENTS

5.3.1 TIMELINE OF FAMILY/FRIENDS SUB-STUDY ASSESSMENTS

Family/friends study procedures and assessments will be performed at 2 study time points (baseline, end of intervention) as outlined in the SoA.

Baseline Study Assessments

Baseline assessments can be completed 3 months prior to starting or on day 1 of the intervention. Assessments can be completed in person, online, or by phone.

1. Questionnaires
2. Qualitative interview (optional procedure)

End of Intervention

End-of-intervention assessments will be completed 1 week prior to and 1 month following the last intervention session.

1. Questionnaires
2. Qualitative interview (optional procedure)

5.3.2 DESCRIPTION OF STUDY ASSESSMENTS

QUESTIONNAIRES

Questionnaires will be self-administered or research staff assisted, in-person, online, or by telephone, based on participant preference. Questionnaires will be completed at baseline and end of intervention.

The following questionnaires will be collected as outlined in the SoA: demographic and acculturation questionnaire, modified brief illness perception and perceived treatment efficacy questionnaires.

QUALITATIVE INTERVIEW – OPTIONAL PROCEDURE

Participation in qualitative interviews is an optional procedure. Participants who opt into this procedure may be contacted at baseline and again at the end of the 6 month intervention to participate in interviews.

All interviews will be conducted by telephone or in-person, according to the participant's preference. The interviews will be audio-recorded (if participant declines this, then notes taken), and transcribed and translated (either by 3rd party or internally be research staff based on participant preference). The interview data will be coded (with a non-identifiable study ID) and stored on the Baylor College of Medicine server.

6. PARTICIPANT DROP-OUT

Intervention of a subject may be discontinued at any time during the study at the discretion of the Principal Investigator for safety. Subjects have the right to discontinue the study and/or withdraw consent at any time.

6.1 INTERVENTION DISCONTINUATION

The decision to end intervention may be made by either the investigator or subject.

Subjects who elect to discontinue the intervention should continue in the study and complete study assessments. Those who discontinue the intervention and have consented to participate in a qualitative interview may be invited to take part in the Main Study Dropout interview.

The Principal Investigator may advise participants to discontinue the intervention for medical reasons. These participants will not be invited to participate in the qualitative interview.

Once the intervention has been discontinued, the subject may not be permitted to resume the intervention. The primary reason for discontinuation must be documented in the subject's source documents and recorded in the EDC (REDCap).

6.2 STUDY DISCONTINUATION

Participants may elect to end study participation. In this situation, an attempt should be made to encourage the participant to complete end of intervention study procedures. Those who end participation and have consented to participate in a qualitative interview may be invited to take part in the Main Study Dropout interview.

6.3 WITHDRAWAL OF CONSENT TO STUDY PARTICIPATION

A subject has the right to withdraw consent at any time upon their own request.

If a subject withdraws consent, the [researchers, staff, and the collaborators on this research?] may still use or disclose information obtained prior to withdrawal. If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this.

While a subject is not required to provide their reason(s) for withdrawing, the investigator must make a reasonable effort to determine the reasons, while fully respecting the subject's rights. If the reason(s) are provided, the primary reason should be documented in the subject's source documents and recorded in the EDC (REDCap).

6.3 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if they repeatedly fail to attend program sessions or study procedures and cannot be reached by the site.

The site must attempt to contact the subject and complete study assessments as soon as possible. The subject should be counseled on the importance of adhering to the study schedule and asked whether they wish to continue in the trial.

Before a subject is considered lost to follow-up, the investigator or designee must make all reasonable efforts to re-establish contact with the subject. This includes making at least three telephone calls and, if necessary, sending a certified letter to the subject's last known mailing address or using local equivalent methods. If the subject cannot be reached, contact efforts should be extended to the subject's relatives or other individuals listed as contacts, as applicable. These contact attempts should be documented in the subject's source document.If the subject remains unreachable by the end of session 16 (end of

intervention), they will be considered to have withdrawn from the trial, with the primary reason recorded as "lost to follow-up."

7. SAFETY & ROUTINE CLINICAL CARE

7.1 INFORMING PARTICIPANTS' PRIMARY PHYSICIANS OF STUDY PARTICIPATION

We will send letters to all participants' physicians to let them know about the planned study participation. In the case of participants who have diabetes, the letters will additionally notify their diabetes providers (standard of care teams) of their participation in the weight loss program, in case diabetes medication changes are required. The letter will include a diabetes management algorithm for weight loss trials for participants' providers to use as they deem appropriate.

7.2 DIABETES MANAGEMENT DURING THE STUDY INTERVENTION

At the beginning of the weight loss program, the PI will advise all participants with type 2 diabetes to review their diabetes management with their physicians to discuss potential impact of calorie restrictions on blood sugar and needed changes to diabetes medications.

Over the duration of the the weight loss intervention, participants with diabetes will be advised to monitor their blood sugars and report episodes of low blood sugar measurements or episodes of symptomatic hypoglycemia to the study team. When reported, the study team will communicate the hypoglycemia to participants' diabetes providers (standard of care teams), so that the diabetes providers can advise appropriate changes to diabetes medications as needed.

8. SAMPLE SIZE RATIONALE & ANALYSIS PLAN

8.1 MAIN STUDY 8.1.1 SAMPLE SIZE JUSTIFICATION

A total of 50 patient participants will be enrolled into the main study (all of whom will receive the intervention). The primary objective of this study is to assess the intervention's feasibility, defined as an average of >8 group counseling sessions attended among the participants over the course of the intervention. A one-sample one-sided t-test at a 5% significance level will provide >80% power to detect that the average number of classes attended will be greater than 8 with 50 participants. This assumes that the SD of classes attended will be 2.8 or less. The rationale for the feasibility outcome is as follows: Studies of Diabetes Prevention Program (DPP) and Look AHEAD Intervention show that higher session attendance is associated with greater degrees of weight loss 1. We define the primary outcome as average number of classes attended >8 because CDC DPP recognition criteria includes attendance of ≥9 sessions in months 1-6 as part of its definition of a program "completer." An evaluation of the DPP over 2015-2018 found that compared with participants who attended <9 sessions, those who attended ≥9 sessions in the first 6 months were 1.8 to 2.2 times more likely to achieve ≥ 5% weight loss from baseline.

8.1.2ANALYSIS PLAN

We will summarize baseline demographic and clinical characteristics using means with standard deviations, medians with minimum and maximum values, or frequencies with percentages. Comparisons between intervention recipients and those in the observational control group will be done using the independent t-test, Wilcoxon rank-sum, Fisher's exact or Chi-square test. To address this study's primary objective (feasibility), a one-sample t-test will be used to test whether intervention recipients attended more than an average of 8 classes. Logistic regression will be used to determine whether there are any differences in retention in the intervention group based on sociodemographic factors (e.g. acculturation, nativity, baseline health literacy), and odds ratios (OR) with 95% CI for retention will be reported.

To address this study's key secondary objective, we plan to compare average weight loss among this study's participants (all of whom receive the weight loss program) with 50 participants of a parallel observational cohort study (derived from H36814) who do not receive this weight loss program (and receive routine Hepatology care). After approval of this intervention feasibility study protocol, we plan to submit an amendment to the H36814 protocol to request data to be used to make this weight loss comparison. If approved, then comparisons between intervention recipients and those in the observational cohort group (derived from H36814) will be done using the independent t-test, Wilcoxon rank-sum, Fisher's exact or Chi-square test. The percent change in weight from baseline to 6 months will be calculated for patients in both the intervention and the observational group. Since the observational control group patients may not have their weight recorded at 6 months, their available weights will be used to calculate the rate of weight change up to 1 year, and this will be used to estimate percent weight change over 6 months. Linear regression will be used to see if the percent change in weight differs between group while adjusting for BMI, age, and any other factors found to be significantly different between the groups or associated with the change in weight.

To address this study's additional exploratory objectives, a general linear mixed model (GLMM) will be used to test the null hypothesis that there is no change in each of the following among intervention patients: liver fat, sugar intake, physical activity, self-efficacy, outcome expectations, motivation, and

self-regulation. A separate model will be used for each outcome, and each GLMM will include a fixed effect for time. Residual analysis will assess model fit, and data transformation will be used to address any departures from model assumptions. P<0.05 will be considered significant.

8.2 QUALITATIVE SUB-STUDY

8.2.1 SAMPLE SIZE JUSTIFICATION

The planned sample size is 5-10 participants in each of the 4 groups: 1) Study Decliners, 2) Main Study Drop-Outs, 3) Main Study Completers with <=8 Sessions Attended, 4) Main Study Completers Who Attended >8 Sessions.

The rationale for the planned sample size is based on thematic saturation, which is the standard method for determining sample size in qualitative research. Thematic analysis is the point at which new themes no longer emerge with progressive interviews. Thematic analysis typically occurs with a sample size of 5-10.

8.2.2 ANALYSIS PLAN

Interviews conducted as part of the qualitative sub-study will provide additional insight into feasibility of the intervention. We will analyze the transcripts for content using Atlas.ti 8 software. We will use framework analysis to address 2 main domains across all 4 planned study groups: feasibility/acceptability of intervention participation and feasibility/acceptability of study participation. Among participants who complete the study, we will additionally conduct framework analysis to address domain of social support for weight loss.

Two members of the research team will independently review each transcript line by line to identify and sort segments of data with similar concepts into distinct categories. We will code data as they amass. After each round of independent coding, the 2 reviewers will convene for review, negotiation, and consensus to resolve discrepancies in coding. We will revise the interview guide to investigate emerging themes. With successive transcripts, we will expand, refine, and apply the coding system to previously coded data. The process of coding and participant recruitment will stop once we have reached thematic saturation in all 3 domains. Dominant themes and sub-themes from the final coding scheme will be presented as study findings. We will choose illustrative quotations to justify the definition and basis of themes. Disagreements about coding decisions will be resolved through group consensus, using a third independent reviewer as a tiebreaker.