A RANDOMIZED CONTROLLED PILOT TRIAL OF A STRUCTURED MOBILE TECHNOLOGY BASED LIFESTYLE PROGRAM VS USUAL CARE FOR PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

Protocol Number: HUM 00153750

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Principal Investigator: Monica Tincopa MD MSc

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Section 1.2	Goal total number of participant was increased from 100 to 120 subjects. Hence, the number of patient in each arm of the study will be 60.	This change is necessary in order to ensure that we have more accurate mean values and provide smaller margin of error.
Section 5.5	Additional recruitment strategies were added. Potential patients will be identified through data direct, EMERSE as well as our general hepatology clinics. Potential participants identified via data direct and our general hepatology clinics will be recruited via phone and text.	Changes will help increase efficiency and speed of recruitment.

Table of Contents

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Randomized Controlled Pilot trial of a Structured Mobile Technology Based Lifestyle Program Vs Usual Care for Patients with Non-Alcoholic Fatty Liver Disease
Grant Number:	AWD007197
Study Description:	Lifestyle interventions remain first line therapy for the treatment of non-alcoholic fatty liver disease (NAFLD). In clinical practice, it is challenging for patients to initiate and maintain these changes. In this randomized clinical pilot trial, we will evaluate impact of a structured mobile technology-based lifestyle intervention program compared to usual care to among patients with NAFLD. We hypothesize individuals randomized to the intervention arm will have significantly improved outcomes compared to usual care, and that the intervention will be feasible, low cost and amenable to large scale implementation.
Objectives:	Primary objective: compare the effectiveness of usual care to a mobile technology based lifestyle intervention on change in liver and metabolic related parameters. Secondary objectives: identify predictors associated with reduction in hepatic steatosis and weight loss.
Endpoints:	Primary Endpoint: change in amount of hepatic steatosis Secondary Endpoints: change in weight, change in physical activity
Study Population:	120 adult patients with NAFLD including steatosis only, non-alcoholic steatohepatitis (NASH) and NAFLD-related compensated cirrhosis seen in the Michigan Medicine Hepatology clinic.
Phase or Stage:	N/A
Description of Sites/Facilities Enrolling Participants:	Michigan Medicine Hepatology Clinics, and patient identified through Data Direct and EMERSE in various local clinics
Description of Study Intervention/Experimental Manipulation:	Personalized adaptive lifestyle intervention program that includes physical activity and nutritional feedback compared to usual care
Study Duration:	18 months
Participant Duration:	13 months

1.2 SCHEMA

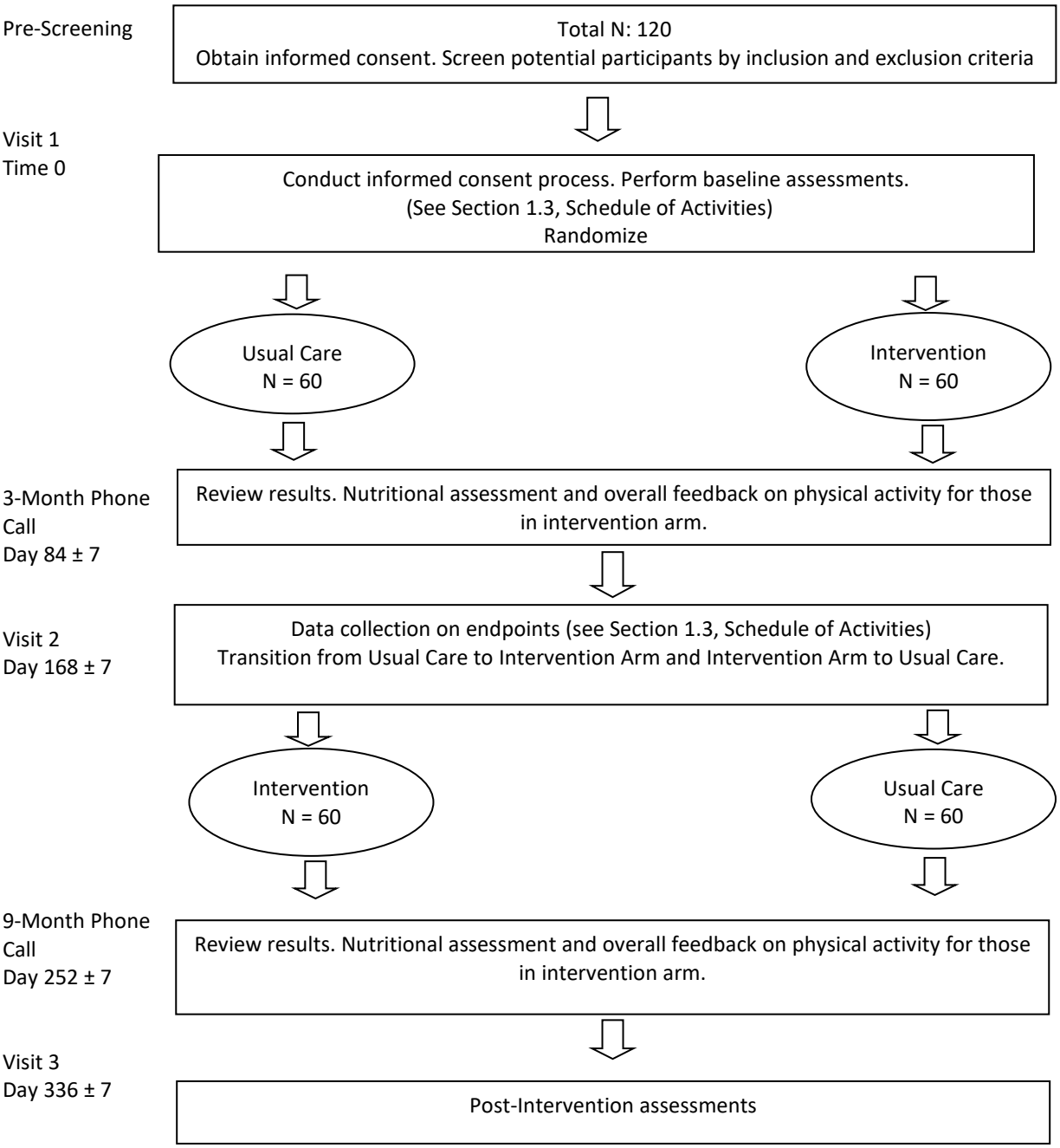

Figure 1. All participants will be enrolled in the study for ~12 months and will complete 3 study visits. Individuals randomized to the Intervenetion arm will have 6 months of intervention followed by 6 months of follow-up to asssess for behavior change maintenance. Individuals randomized to the Usual Care Waitlist will be followed for 6 months, after which they will start a 6-month intervention period.

1.3 SCHEDULE OF ACTIVITIES

Table 1 - Arm 1 - active intervention w/follow up

OnCore Calendar Segment	Pre-study	Consented OnStudy OnArm/OnTreatm	On treatment	On FollowUp	OffStudy
Study Timeline	Pre-screening (Pre-consent)	Visit 1 Day 1	Phone Call-Intervention Arm Day 84 ±7	Visit 2 Day 168 ±14	Visit 3 Day 336 ±21
EMR Review Eligibility	X				
Informed Consent		X			
Demographics		X			
Clinical history		X			
Randomization		X			
Provide FitBit and Instruction to Intervention Arm		X		X	
Outcome Evaluation					
Vitals + Anthropometrics: blood pressure, height, weight, waist and hip circumference		X		X	X
Blood Work:[1] hepatic panel, platelets, A1c, fasting insulin, glucose, lipid panel		X		X	X
6MWT		X		X	X
Hand Grip Strength		X		X	X
Quality of Life Questionnaire		X		X	X
Physical Activity Survey (IPAQ)		X		X	X
Motivation to Change Questionnaire		X		X	X
Dietary Survey		X	X	X	X
Dietician Assessment[2]		X			
VCTE [1]		X		X	X
MRE1[1,3]		X		X	
Exit Interviews				X	X
Adverse Events Reporting		X	X	X	X

Table 2. Arm II - wait list control; receives intervention after visit 2

OnCore Calendar Segment	Pre-Study	Consented OnStudy	OnTreatment		Off Study
Study Timeline	Pre-screening (Pre-consent)	Visit 1 Day 1	Visit 2 Day 168 ±7	Phone Call-Intervention Arm Day 252 ±14	Visit 3 Day 336 ±21
EMR Review Eligibility	X				
Informed Consent		X			
Demographics		X			
Clinical history		X			
Randomization		X			
Provide FitBit and Instruction to Intervention Arm		X	X		
Outcome Evaluation					
Vitals + Anthropometrics: blood pressure, height, weight, waist and hip circumference		X	X		X
Blood Work:[1] hepatic panel, platelets, A1c, fasting insulin, glucose, lipid panel		X	X		X
6MWT		X	X		X
Hand Grip Strength		X	X		X
Quality of Life Questionnaire [4]		X	X		X
Physical Activity Survey (IPAQ) [4]		X	X		X
Motivation to Change Questionnaire [4]		X	X		X
Dietary Survey [4]		X	X	X	X
Dietician Assessment[2]		X			
VCTE [1]		X	X		X
MRE1[1,3]		X	X		
Exit Interviews			X		X
Adverse Events Reporting		X	X	X	X

[1]Baseline results can be abstracted from medical record if performed within prior 6 months and <5% weight change since that time. Otherwise, VCTE will be performed +/- 14 days from enrollment. Hepatic panel and platelet count are standard of care measures. Remainder of imaging and laboratory data will be research costs.
[2]Can be done +/- 14 days from enrollment in person or via telephone
[3] Only done in half of patients due to cost, determined by computer randomization with stratification according to liver disease stage (cirrhosis)
[4] If not enough time during enrollment, participants will be sent a link via email to complete the surveys within 14 days from enrollment date.
EMR, electronic medical record; 6MWT, 6 minute walk test; IPAQ, International Physical activity Questionnaire; VCTE, vibration controlled transient elastography; MRE, magnetic resonance elastography

2 INTRODUCTION

2.1 STUDY RATIONALE

The only proven curative therapy for non-alcoholic fatty liver disease (NAFLD) is improvement in nutrition and increased physical activity targeted to weight loss. In clinical practice, the majority of patients have limited success with making these behavior changes and sustaining them. There is a critical knowledge gap related to the optimal design of lifestyle interventions for NAFLD patients and predictors of response to specific types of treatment interventions. This study aims to evaluate the impact of a mobile technology-based lifestyle intervention program compared to usual care for patients with NAFLD.

2.2 BACKGROUND

NAFLD is a highly prevalent form of chronic liver disease that is caused by fat build-up in the liver. This condition is associated with obesity and underlying metabolic syndrome, and is estimated to affect 25% of adults worldwide. Over time, the fat deposition in the liver can cause inflammation, liver injury and the development of fibrosis (scar tissue) that can progress to cirrhosis and end-stage liver disease. Additional significant associated morbidity and mortality includes development of hepatocellular carcinoma, increased risk of cardiovascular events, and poor health-related quality of life (HRQOL).(1-3) Thankfully, there is a proven curative therapy for NAFLD. A 3-5% reduction in body weight decreases steatosis; a 10% reduction can resolve steatosis, inflammation and fibrosis.(4) Exercise alone, independent of weight loss, has also been shown to reduce steatosis.(5) As a result, lifestyle changes, improved nutrition and physical activity, are first line therapy for NAFLD.(1) Despite the liver and multi-system benefit of this approach and the consequences of untreated NAFLD, the uptake and maintenance of lifestyle interventions is extremely limited in practice. The precise barriers to and reasons for limited uptake of lifestyle changes among individuals with NAFLD are poorly understood. Relatedly, there is an important knowledge gap regarding the optimal design of structured lifestyle programs that would have real-world effectiveness and are low cost, sustainable and scalable tailored to patients with NAFLD. This lack of a standardized approach for lifestyle interventions also has implications for pharmacotherapy trials where variable “placebo effects” stemming from heterogeneous control group implementation of diet and exercise recommendations confound the interpretation of efficacy of these medications.(6)

While highly regimented lifestyle programs have shown to be efficacious, they are often costly, not accessible to many patients, and not amenable to long term sustainability and scalability.(7) Data from the obesity literature indicates that programs that remove logistical barriers (time constraints, cost) and increase the frequency of interactions/ follow-up with real-time feedback have a higher likelihood for real world effectiveness. Mobile technology based lifestyle programs encompass many of these features and have proven to be effective for weight loss among cohorts with similar phenotypes.(8) Preliminary data from our initial pilot trial of a mobile technology-based lifestyle program among NAFLD patients suggest feasibility and efficacy in terms of positive impact on weight loss, physical function, HRQOL and liver and metabolic parameters. Data from a small cohort of NAFLD patients also demonstrated a mobile technology program (text messaging) was effective in promoting weight loss (mean decrease 11-lb compared to none in control group).(9)

In order to assess outcomes of interest, we will employ validated non-invasive biomarkers to assess changes in hepatic steatosis and fibrosis. This includes VCTE, an ultrasound based test that can capture both amount of steatosis via controlled attenuation parameter (CAP) and fibrosis via liver stiffness

measurements. More recently, MRI based imaging tests, MR elastography (MRE) has been shown to have excellent accuracy for assessment of both fibrosis (elastography) and hepatic steatosis (via proton density fat fraction – PDFF). (10) Lifestyle interventions in the general obesity literature and among NAFLD cohorts have been shown to have excellent safety profile with no to minimal adverse events, with primary concern being falls or other musculoskeletal related injuries.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The risks related to dietary changes and increase in physical activity are minimal, with overall systemic benefit improvements likely far outweighing any potential risks. So long as dietary restriction does not involve > 30% reduction in total caloric intake per day, risks to calorie restriction should be minimal. (11) Regarding physical activity, the overwhelming majority of individuals will be able to partake in a walking program with minimal to no risk. More vigorous exercise will be implemented based on baseline fitness and other factors that may impact potential to achieve higher METS. Potential, but unlikely risks include falls or other musculoskeletal injuries resulting from physical activity, or cardiac events among individuals with cardiac disease who engage in overly ambitious exercise regimens in an unsupervised setting. In terms of survey instruments, these risks are also minimal and rare, but include the potential for feelings of discomfort or anxiety related to answering personal questions. Participants will be able to opt out of answering questions that are discomforting to them. For participants completing MREs, there is a risk of feeling anxious or claustrophobic, transient changes in hearing due to clanging of the machine (rare), and risk related to indwelling metal that can be impacted by the machinery, but this will be addressed with proper screening. Lastly there is a risk of breach of confidentiality and privacy associated with being in the study, including potential breach of the FitBit app.

2.3.2 KNOWN POTENTIAL BENEFITS

Incorporating healthy eating and exercise has been demonstrated to improve HRQOL and multiple systemic metabolic diseases. (12)

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The potential risks are minimal as outlined above and are far outweighed by possible benefits.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Compare the effectiveness of usual care to a mobile technology based lifestyle intervention on change in liver and metabolic related parameters.	Reduction in amount of hepatic steatosis (≥5% overall reduction in CAP score) at 6 months.	Hepatic steatosis is a liver specific outcome that has been shown to improve with diet and exercise and is associated with risk of downstream clinical outcome such as development of NASH and cirrhosis.
Secondary		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Improvements in other liver-specific and metabolic outcomes	weight loss, increase in total physical activity (based on step counts)	Weight loss has been associated with histologic improvements in NAFLD and NASH. Physical activity has been shown to improve fibrosis, liver enzymes, metabolic parameters and HRQOL.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This randomized clinical pilot trial will compare a mobile technology-based lifestyle intervention to a wait-list control group receiving usual care for adult patients with NAFLD. The intervention will use FitBit to track and promote physical activity through tailored longitudinal feedback. Patient will also receive nutritional counseling with serial nutritional assessments. The primary endpoint will be change in amount of hepatic steatosis. Secondary outcomes include changes in weight and physical activity (assessed by trend in step counts). A wait-list control design will be applied. 60 Patients will be randomized to the intervention arm for 6 months and 60 to usual care (the wait-list control). Those initially randomized to the intervention arm will then transition to a 6-month post intervention monitoring period to assess maintenance of behavior change and sustainability of impact on outcomes of interest. Individuals initially randomized to usual care, will transition to the intervention at month 6 for a total of 6 months.

The intervention arm will receive tailored physical activity and nutritional counseling, and the waitlist control arm which will follow usual and customary care for NAFLD patients attending our Heptology clinic for 6 months and then receive the 6-month intervention.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This trial will incorporate a wait-list control that will allow us to maximize our ability to assess the primary outcome (by using a pre-post intervention analysis). The 6-month post-intervention follow-up among those initially randomized to the intervention will allow us to assess maintenance of behavior change.

4.3 JUSTIFICATION FOR INTERVENTION

Multiple studies in general obesity research and specifically among patients with NAFLD have shown that patients should aim to achieve ≥150 min/week of moderate intensity physical activity. For diet, the majority of studies have recommended a total caloric reduction of 30% in obese and overweight patients in order to achieve weight loss. We will track total amount of physical activity time and change in nutritional content as part of this intervention.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Age 18 or older
4. Diagnosis of NAFLD or NASH based on: liver biopsy (within past 24 months) or imaging [ultrasound (US), vibration controlled transient elastography (VCTE), cat scan (CT), or magnetic resonance imaging (MRI)] within past 24 months
5. Ability to communicate in English as their primary language.
6. Access to mobile phone/tablet/ or computer compatible with FitBit application and ability to use said device and application.
7. Ability to participate in physical activity (reports ability to walk at least several blocks unassisted).

5.2 EXCLUSION CRITERIA

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

1. Other causes of liver disease: Alcohol related liver disease (defined as an average 14 or more drinks per week in men and 7 or more drinks per week in women over the past 12 months); viral hepatitis, autoimmune liver disease, hereditary forms of liver disease, etc.
2. Medications known to cause hepatic steatosis or other alternative causes of hepatic steatosis: mediations include steroids, tamoxifen, amiodarone, highly active anti-retroviral therapy (HAART), valproate, methotrexate. Other causes of hepatic steatosis include chronic total parenteral nutrition (TPN), severe rapid weight loss.
3. Current or prior history of decompensated cirrhosis: variceal bleeding, ascites, hepatic encephalopathy, or hepatocellular carcinoma.
4. Inability to make dietary modifications due to significant medical co-morbidity (including but not limited to severe, uncontrolled diabetes).
5. Participation in a pharmacologic clinical trial for NAFLD/NASH.
6. Plans for invasive procedures or other regimented lifestyle programs for weight reduction (i.e. bariatric surgery, other structured nutrition or exercise program such as University Metabolic Fitness Program, University of Michigan Medical Weight Loss Program, Weight Watchers, etc)
7. Current use of weight reduction medications or supplements.
8. Active substance abuse or psychiatric disease which limits patient's ability to follow study protocol.
9. Recent cardiovascular event (within last 3 months) including myocardial infarction, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), cerebrovascular

accident (CVA), transient ischemic attack (TIA), severe cardiac valve disease, complex arrhythmias, class II-IV New York Heart Association (NYHA) heart failure
10. Pregnancy based on self-report
11. Individuals randomized to MRE cannot have non-MRI compatible metal in their body or severe claustrophobia.

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants will be asked to partake in the lifestyle intervention as outlined in detail in the study protocol. They are to refrain from starting any of the following treatments while enrolled in the study:

- Any new lifestyle or non-pharmacologic therapy for weight loss
- Any new exercise program
- Any medication or supplement for weight loss or appetite control

Participants are asked to let the study team know about any new lifestyle or non-pharmacologic therapies started for other reasons, e.g. physical therapy for knee pain or osteoarthritis. Likewise, participants should tell the study team about any new medications that might affect weight (e.g. metformin or some SSRIs, etc.)

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a lack of biopsy or imaging evidence of NAFLD within the designated time frame may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Potential participants will be identified through Data Direct, EMERSE or via screening of patients with NASH/NAFLD in our general hepatology clinics. Eligible participants will be recruited via phone, text or from our general hepatology clinics at the time of a routinely scheduled outpatient clinic appointment. Individuals who complete the entire study will receive $75, with $25 provided after the completion of each study visit and associated data collection for that visit.

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

6.1 STUDY INTERVENTION(S)

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

This is a randomized trial comparing a structured mobile technology-based lifestyle intervention compared to usual care.

Intervention

-Education: Patients in the intervention arm will receive our NAFLD educational folder with an overview of contents by study staff. The folder includes: 1) NAFLD disease information including diagnosis, clinical manifestations, natural history and treatments; 2) NAFLD nutritional recommendations including sample menus; 3) NAFLD physical activity recommendations including walking programs and physical activity logs; 4) weight tracking logs; and 5) resources for diet and exercise programs.

-**Physical Activity**: All participants in the intervention arm (N=60) will receive a FitBit Zip for monitoring of step counts. The Fitbit wirelessly syncs data from the tracker to the Fitbit software or app. Study staff will assist with downloading the software and will instruct participants to wear their FitBit during waking hours every day. At any time if the participant has questions or problems regarding the use of the FitBit, a study staff member can be contacted. Study staff will retrieve users' step count data for analysis weekly and will provide subject with personalized feedback on physical activity with tailored step count goals (10% increase per week with max increase 800 steps per week to a maximum of 10,000 steps/week) and motivational messaging via e-mail. Patients with consecutive days without data recorded or with other signs of low FitBit usage (days with minimal step counts) will be contacted by study staff via e-mail or phone if necessary to encourage use. Feedback will occur weekly for the first 3 months of the intervention and then transition to biweekly for the last 3 months. Participants will also complete the short-version IPAQ for physical activity at enrollment, 6 month and 12 month follow-up visits.

-**Nutrition**: Patients in the intervention arm will have a nutritional assessment by a GI nutritionist specializing in NAFLD either at the enrollment visit if time allows, or in a separate in person or phone assessment within the first 2 weeks of enrollment. All patients will also complete the "Starting the Conversation" nutritional questionnaire for patients with metabolic disease at enrollment, 6 month and 12 month follow-up visits.(15)

Usual Care

At our center, patients with NAFLD /NASH without decompensated cirrhosis are seen every 6-12 months. Visits are approximately 15-20 minutes and consist of review of BMI/weight, recent hepatic panel and Fibroscan if ordered. Management typically consists of a breif overview of lifestyle changes including improvements in nutrition and physical actiity. Vitamin E is prescribed In a small proportion of patients. A similarly small proportion of patients are formally referred to and subsequently evaluated by a nutritionist.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

The dieticians are RDs with specific expertise in caring for patients with liver disease. Study staff will be trained on how to provide tailored feedback on physical activity (step count goals). They had demonstrated proficiency in following standard procedures.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants in this trial will be randomized to either the intervention arm (tailored physical activity and nutritional counseling) or a wait-list control arm that receives usual care for 6 months, after which they will receive the intervention (for 6 months). Neither participants nor interventionists are blinded to study arm.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Adherence will be assessed by the following:
-Completion of all study visits and data collection elements
-Percentage of days with valid FitBit data (>300 steps per day as defined in behavioral health literature). Step count data will be assessed weekly for each participant.

6.5 CONCOMITANT THERAPY

Participants can continue any treatments that are not listed as part of the exclusion criteria for this study.

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

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The minimum data to be collected at the time of study intervention discontinuation will include the following:

- Weight and anthropometrics, laboratory studies, HRQOL and VCTE if possible.
- Download of all available Fitbit data

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention

- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study intervention for 30 days/4 weeks
- Start of new therapy/program that is not allowed while enrolled in this study

The reason for participant discontinuation or withdrawal from the study will be recorded on the appropriate CRF. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 1 scheduled study visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit within 2 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the study team will make every effort to contact with the participant (where possible, 3 telephone calls, emails or text messages). These contact attempts should be documented in the participant's research record.
- Should the participant continue to be unreachable, 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

-Baseline & Outcome Assessments

1) Demographics and Medical History: alcohol use, components of metabolic syndrome, diabetes, thyroid disease, depression, cirrhosis, NAFLD vs NASH.

2) Physiologic Measures: blood pressure, weight, BMI, waist circumference, waist to hip ratio

3) Physical Function and Frailty Measures: 6 Minute Walk Test (6MWT) to assess baseline physical function (validated among patients with chronic liver disease)(13) and hand grip strength;(14)

4) HRQOL and Stages of Change: CLDQ-NAFLD for HRQOL and the validated motivation to change behavior questionnare.(16)

5) Laboratory studies: hepatic panel, platelet count, lipid panel, glucose and hemoglobin A1c (abstracted if obtained within the last 6 months; otherwise ordered at time of clinic visit). If laboratory studies are ordered for study purposes, blood for hepatic panel, lipid panel and glucose will be obtianed in 1 serum separator tube (SST) (3mL). One lavender tube will be used to collect specimen for platelet count (3mL), and another 1 lavender tube will be used for hemoglobin A1c. The total amount of blood drawn from patients will not exceed 20 mL, and will be kept within the IRB restrictions.

6) Hepatic Imaging: all patients will complete a fibroscan to assess liver stiffness and CAP measurements unless performed within prior 6 months. Historical results for prior testing will only be used if patients had not had >5% weight loss in prior 12 months. Due to cost limitations, a total 50 patients will have MRE with

PDFF. MRE exams will be evenly assigned by computer randomization with stratification according to liver stage (cirrhosis, no cirrhosis) and subcategory (NAFLD vs NASH) in each arm.

Phone Call: Patients receiving the intervention will receive a phone call to review baseline data results after 3 months of intervention. They will also complete a second nutritional questionnaire. Patients will also be given detailed feedback and recommendations on step counts and nutrition thus far.

8.2 SAFETY ASSESSMENTS

In order to screen for potential study participants, our clinical research staff with review the electronic health record (EHR) in compliance with HIPPAA protocol.

Individuals enrolled in the study will complete the following procedures/evaluations to monitor clinical status and occurrence of adverse events:

- **Physical examination:** weight, waist and hip circumference.
- **Vital signs:** blood pressure
- **Radiographic or other imaging assessments:** VCTE and MRE
- **Biological specimen collection and laboratory evaluations**: Platelet count, hepatic panel, lipid panel (fasting), hemoglobin A1c, fasting insulin
- **Assessment of adverse events:** to be assessed at 3-month phone call, 6 and month follow-up visits. Patients will also be asked to self-report AEs of interest (with focus on falls and other activity-related musculoskeletal injuries) during weekly eHealth communications.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the PI, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an 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

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 AEs must have their relationship to study intervention assessed by the PI. She will evaluate the event based on temporal relationship of the event to the study intervention or research procedures, and 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 results, occurs in a plausible time relationship to participation in the study intervention and cannot be explained by other factors (e.g. concurrent disease, other treatments or activities or action).
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The event occurs within a reasonable time relative to participation in the study intervention, is unlikely to be attributed to concurrent disease or other factors.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time relative to participation in the study intervention). 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 whose temporal relationship to participation in the study intervention makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which underlying disease or other factors provide a plausible explanation for the event occurrence.
- **Not Related** – The event is completely independent of the study intervention, and/or evidence exists that the event is definitely related to another reason.

8.3.3.3 EXPECTEDNESS

The primary investigator will be responsible for determining whether an 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 intervention.

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

The occurrence of an AE or SAE may come to the attention of the study team during study visits and routine study participant contact throughout their participation in the study.

All AEs including (including SAEs) will be captured on the appropriate CRF. Information to be collected includes event description, date of onset, PI's assessment of severity, relationship to study intervention, and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical 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 related to their NAFLD/NASH deteriorates at any time during the study, it will be recorded as an AE. Changes in condition in unrelated medical issues with be documented but not reported.

each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Adverse event reporting will follow the protocol outlined above.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The PI will follow the IRBMED standard reporting schedule for SAEs (*https://az.research.umich.edu/medschool/guidance/adverse-event-reporting*). We will report any serious adverse event considered study intervention related.

All SAEs will be followed until satisfactory resolution or until the PI deems the event to be chronic or the participant is stable.

8.3.7 REPORTING OF PREGNANCY

If participant becomes pregnant during study period, participation will end at that time.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

The Office for Human Research Protections (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 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.

For guidance on Michigan Medicine UaP guidelines, refer to *https://az.research.umich.edu/medschool/guidance/adverse-events-aes-other-reportable-information-and-occurrences-orios-other* .

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UaP) to IRBMED (*https://az.research.umich.edu/medschool/guidance/adverse-events-aes-other-reportable-information-and-occurrences-orios-other*) and will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the HUM 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 IRBMED according to the standard reporting schedule (within 7-14 days depending on whether it's life threatening serious event vs. other serious adverse event: *https://az.research.umich.edu/medschool/guidance/adverse-event-reporting*)
- Any other UP will be reported to IRBMED within 14 days of the investigator becoming aware of the problem.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Any UaP that results in a change to the study design, procedures or risks will be addressed as necessary in an amended consent document. Participants will be asked sign the new consent document as indicated.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint:
We hypothesize that participants who complete the lifestyle intervention (as defined by completing the 6 month return visit and data collection) will achieve reduction in amount of hepatic steatosis (≥5% reduction in CAP), with those achieving higher percentage weight loss having larger reductions in amount of steatosis.

Secondary Efficacy Endpoints:
We hypothesize that subjects in the intervention arm will be more likely to achieve weight loss and increase their level of physical activity at 6-month compared to usual care.

9.2 SAMPLE SIZE DETERMINATION

Sample size calculations will be made based on the total N for the cohort. Enrollment of 120 patients in the intervention should provide adequate power to assess for parameters associated with ≥5% reduction in steatosis and weight loss using 80% power, alpha 0.05. We anticipate a dropout rate of up to 20%.

9.3 STATISTICAL ANALYSES

9.3.1 GENERAL APPROACH

Categorical data will be presented as percentages. Continuous data will be presented as medians with interquartile range.

For inferential tests, the p-value of 0.05 will be considered significant; 95% confidence intervals for statistical significance (Type I error) and two-tailed tests will be used.

Nonparametric tests will be used to analyzed any non-normative data.

9.3.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary outcome is change in steatosis. This will be assessed by VCTE controlled attenuation parameter (CAP). A ≥5% *reduction* in CAP score at 6-months and maintenance at 12 months as this has been associated with clinically meaningful improvements in outcomes.

For individuals with missing data (participants who do not complete follow-up imaging), we will analyze as modified intention to treat and a separate analysis among those who completed all data collection elements.

Subjects will be analyzed according to a modified intention to treat analysis. Individuals who were randomized but never provided FitBit data will not be included in the final analysis

9.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Analysis of secondary endpoints are not dependent on findings of primary endpoint.

-% weight loss: at month 6
-Physical activity: ≥10% increase in total minutes/week of physical activity based on IPAQ at month 6

9.3.4 SAFETY ANALYSES

A summary statistic of any adverse events will be provided.

9.3.5 BASELINE DESCRIPTIVE STATISTICS

Baseline descriptive statistics of demographics, clinical characteristics, laboratory and imaging tests will be performed.

9.3.6 SUB-GROUP ANALYSES

The primary endpoint will also be analyzed according to presence of NASH and cirrhosis.

9.3.7 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual patient data will be listed by measure and time point to allow for a pre-post comparison.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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 are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRBMED-approved and the participant will be asked to read and review the document. The study team will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or others, or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the study team. This confidentiality is extended to cover all lab tests and study procedures, and study interactions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No

information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor and/or consent of the participant.

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

Authorized representatives of the sponsor, representatives of IRBMED and other regulatory committees may inspect all documents and records required to be maintained by the investigator, including but not limited to, research and medical records (office, clinic, or hospital) for the participants in this study.

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 our eResearch application and IRBMED.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Michigan Medicine. Participant contact information and study data will be maintaind in a HIPAA compliant study database (REDCap). Individual research records will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected. After publication of the primary manuscript, all study databases will be de-identified and archived at University of Michigan.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the University of Michigan. After the study is completed, the de-identified, archived data will be stored at the University of Michigan for use by the research team. Permission to store data will be included in the informed consent.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Monica Konerman , MD MSc, Clinical Lecturer
University of Michigan
1500 E. Medical Center Drive Ann Arbor, MI 48109
734-936-4000
Konerman@med.umich.edu

10.1.5 QUALITY ASSURANCE AND QUALITY CONTROL

We will perform internal quality management of study conduct and data. An individualized quality management plan will be developed to describe a site's quality management.

Quality control procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the PI for clarification/resolution.

- The study team will self-monitor for data integrity
- Regular data audits will occur throughout each year of the project, roughly once a quarter
- The REDCap database will be configured with data validation rules

10.1.6 DATA HANDLING AND RECORD KEEPING

10.1.6.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the study staff under the supervision of the PI who is ultimately responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All study documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopy CRFs will be filed in individual study records and electronic data capture will occur within the REDCap database (a 21 CFR Part 11-compliant data capture system). All study data whether captured on a paper CRF or electronically will stored in the study database. It uses the same login credentials as the EMR, and is password protected. We will incorporate internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the EMR, study CRFs or other sources.

10.1.7 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the study protocol. The noncompliance may be either on the part of the participant or the study team. Protocol deviations can be inadvertent (i.e. participant forgot to fill out a survey so data is missing) or deliberate (e.g. study team elected not to do 6MW because participant reports not being up to the task).

Deviations related to increased participant risk or major impact on data integrity be reported to IRBMED.

It is the responsibility of the study team and PI to follow the protocol and document deviations. Reporting of protocol deviations within 7-14 days (*https://az.research.umich.edu/medschool/guidance/protocol-deviations-exceptions-violations*).

ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HIPAA	Health Insurance Portability and Accountability Act
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
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
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.2 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
2.0	10-31-2019	Change of Principal Investigator's name	N/A
2.0	10-31-2019	Extended the time frame in which the VCTE can be done up to 14 days from enrollment date. If not enough time during enrollment, participants will be sent a link via email to complete the surveys within 14 days from enrollment date.	Extending the time frame in which participants can have the VCTE up to two weeks from their enrollment into the study will make participation in the study more convenient for subjects by shortening the length of the visit. Additionally, in the instances where VCTE is not available on the days or times subjects are enrolled into our study, this will give us the flexibility to schedule them in for a different day. Allowing participants to complete the surveys online will help increase efficiency and speed of enrollment.

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