Noom Health for Weight Management
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Noom Health for Weight Management

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Principal Investigator: Thomas Hildebrandt, PsyD

Sponsor: <Noom, Inc>

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CONFIDENTIALITY STATEMENT

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 Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as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

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the <specify NIH Institute or Center (IC) > Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

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

Effective Date: 9/1/2022
End Date:10/18/2022

INVESTIGATOR'S SIGNATURE

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

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name: Thomas Hildebrandt

Title: Associate Professor

Investigator Contact Information
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1 PROTOCOL SUMMARY

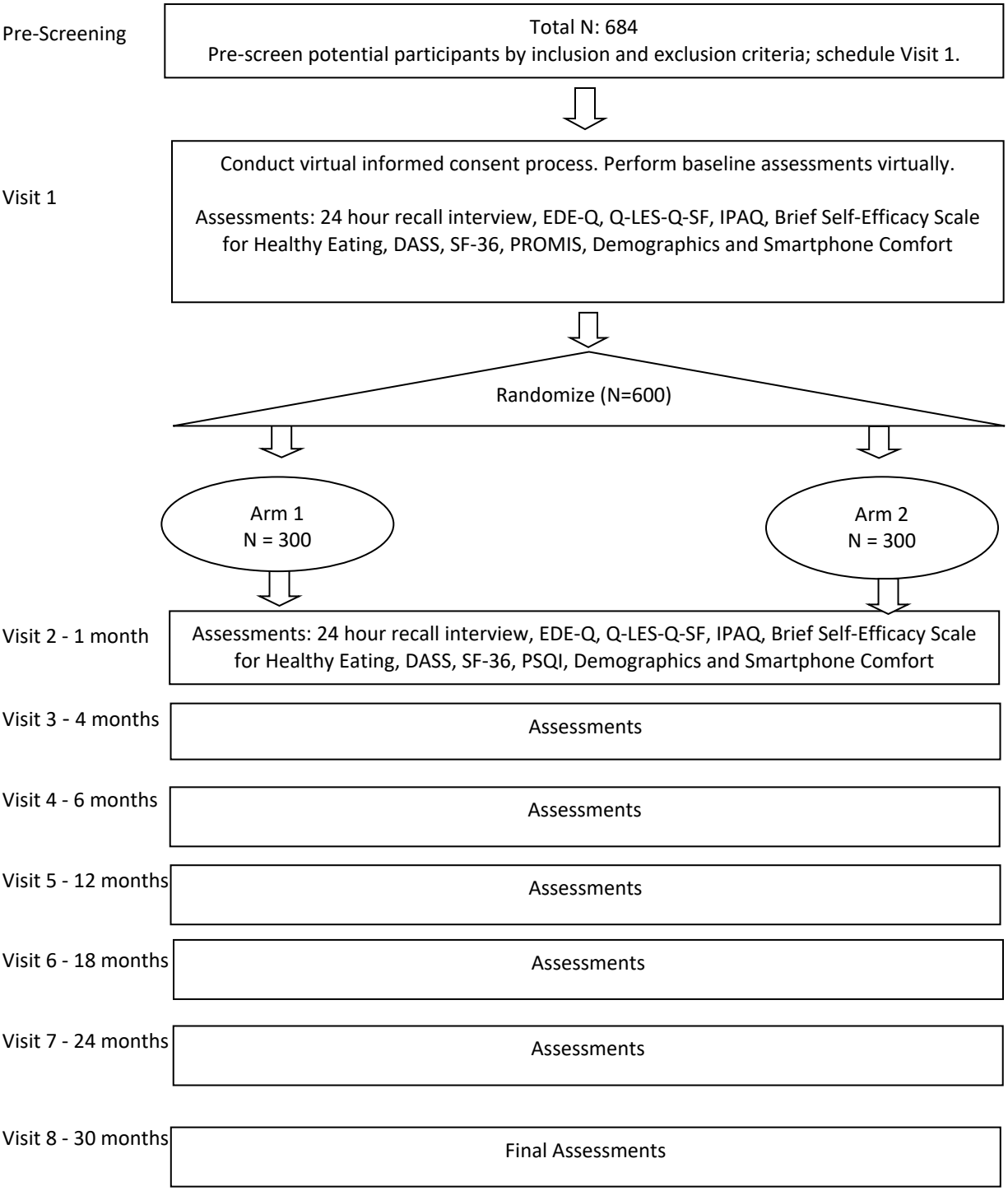
1.1 SYNOPSIS

Title:	Noom Health for Weight Management
Study Description:	Overweight and obesity affect as many as one-third of the population of the United States. Excess weight represents a serious public health concern, as overweight and obesity are associated with an increased risk of medical sequelae (e.g., high blood pressure, sleep apnea, COVID-19, etc.). Although behavioral treatments for obesity are generally effective, reductions in weight are typically modest and largely not maintained over the long-term. This study will test a successful commercially available weight loss phone app (Noom Health) in comparison to a Digital Education program (Noom Digital Health) for weight loss, quality of life, psychosocial functioning, and self-reported health status. We will recruit 600 subjects and randomize them to receive Noom Health vs. Digital Control. Baseline measures will include demographics, psychosocial measures, height/weight, weight loss history/practices, health care practices/utilization, and quality of life. We will conduct remote scheduled direct entry interview and self-report questionnaire data at 8 time points (Screening/Baseline, 1 month, 4 months, 6 months, 12 months, 18 months, 24 months, and 30 months). Weight data will be collected by video observed scale. Digital scales will be provided for those who do not have access.
Objectives:	Primary Objective: The goals of the study are to use the Noom smartphone platform to help individuals with weight loss, quality of life, psychosocial functioning, and self-reported health status. Secondary Objectives: We will test the efficacy of this platform against a Digital Education program in a cohort of patients.
Endpoints:	We will conduct remote scheduled direct entry interview and self-report questionnaire data at 8 time points (Screening/Baseline, 1 month, 4 months, 6 months, 12 months, 18 months, 24 months, and 30 months). Weight data will be collected by video observed scale. Digital scales will be provided for those who do not have access
Study Population:	Overweight and obese adults aged 18-60 years.
Phase or Stage:	*Phase II trial.*
Description of Sites/Facilities Enrolling Participants:	The team at the Icahn School of Medicine at Mount Sinai (ISMMS) is responsible for recruitment, consenting, consulting on the coaching intervention, and data collection and analysis. Research procedures are expected to occur remotely with ISMMS staff.

Description of Study Intervention/Experimental Manipulation:	Participants will use the Noom app for 6 months of intervention and 6 months of maintenance (12 months total).
Study Duration:	3-5 years
Participant Duration:	30-32 months

1.2 SCHEMA

Flow Diagram *(randomized controlled trial)*



1.3 SCHEDULE OF ACTIVITIES

The schedule of activities (SOA) provided below outlines the expected activities for each research visit. Participants are expected to be enrolled in the study for 2.5 years and complete all research visits via a HIPAA compliant video platform (Zoom) and REDCap.

	Pre-screening (Pre-consent)	Visit 1 Day 1	Visit 2 Day 30 ± 42	Visit 3 Day 121 ± 42	Visit 4 Day 182 ± 42	Visit 5 Day 365 ± 42	Visit 6 Day 547 ± 42	Visit 7 Day 730 ± 42	Visit 8 Day 912 ± 42
EMR Review Eligibility	X								
Informed Consent		X							
Demographics		X							
Height, Weight,		X	X	X	X	X	X	X	X
Outcome Evaluation									
Depression, Anxiety, Stress Scale		X	X	X	X	X	X	X	X
Quality of Life Questionnaire		X	X	X	X	X	X	X	X
ASA24		X	X	X	X	X	X	X	X
Eating Disorder Examination Questionnaire		X	X	X	X	X	X	X	X
International Physical Activity Questionnaire		X	X	X	X	X	X	X	X
PROMIS Sleep Impairment		X	X	X	X	X	X	X	X
Short Form Health Survey		X	X	X	X	X	X	X	X

Brief Self-Efficacy Scale for Healthy Eating		X	X	X	X	X	X	X	X
Randomization		X							
Control & Experimental Interventions – Noom App vs Digital Control		X	X	X	X	X			
Adverse Events Reporting		X	X	X	X	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

The goals of the study are to use the Noom smartphone platform to help individuals with weight loss, quality of life, psychosocial functioning, and self-reported health status. In addition, we will test the efficacy of this platform against a Digital Education program in a cohort of patients.

We will conduct a large test (n=600) where participants are randomized to receive Noom Health vs. Digital Control (Noom Digital Health). Baseline measures will include demographics, psychosocial measures, height/weight, , weight loss history/practices, health care practices/utilization, and quality of life. We will conduct remote scheduled direct entry interview and self-report questionnaire data at 8 time points (Screening/Baseline, 1 month, 4 months, 6 months, 12 months, 18 months, 24 months, and 30 months). Weight data will be collected by video observed scale. Digital scales will be provided for those who do not have access.

2.2 BACKGROUND

Overweight and obesity have reached epidemic proportions in the United States. Excess weight represents a serious public health concern, as overweight and obesity are associated with an increased risk of medical sequelae (e.g., high blood pressure, sleep apnea, COVID-19, etc.). Although behavioral treatments for obesity are generally effective, reductions in weight are typically modest and largely not maintained over the long-term.

Behavioral weight loss programs are typically provided with weekly nutritional counseling because of the numerous required changes to diet and physical activity; however, this type of intervention is costly and requires the availability of trained professionals with advanced degrees. A smartphone app to translate behavioral weight loss principles into a digestible and manageable intervention helps to overcome limitations such as costs, availability of trained professionals, and time-burden and scalability that make behavioral weight loss less practical and available. The Noom platform improves the accessibility of expert guidance for individuals interested in weight loss and facilitates maintenance through low-burden smart phone engagement.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

- Anxiety related to eating or change in weight status
- Emotional discomfort during assessments
- Possible loss of confidentiality

2.3.2 KNOWN POTENTIAL BENEFITS

There are no anticipated direct benefits to participants. Some participants may improve their diet/exercise, and data from the study may help to identify individuals who benefit from a behavioral weight loss app in comparison to other interventions.

With increasing numbers of individuals with overweight and obesity, and few effective behavioral treatment options, understanding factors that influence outcomes could be broadly beneficial to society.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Participants may feel some anxiety related to the lifestyle changes that the intervention asks of them. Noom coaches are trained in managing these difficult situations as part of a standardized Noom Coach Academy lead by licensed clinical psychologist (Andreas Michalaedes, PhD) who maintains the academy training and regulation. Participants are free to end their participation at any point in the study.

Participants will be told that they are free to not respond or to terminate involvement with the assessment at any time, with no adverse consequences. If a participant appears to be distressed during assessments, research staff will halt the interview and offer to proceed at another time. The interview will only recommence when and if the participant reports feeling capable of doing so. The interviews during the course of the study involve no specific risk or discomfort beyond those of a standard clinical interview. Interviews will be conducted by experienced and well- trained staff sensitive to these issues.

There is a slight risk that research records (questionnaires, consents) might be obtained by persons not authorized to do so. There is a slight risk that research data files might be compromised, and obtained or viewed by unauthorized persons. As described in the data storage section, we have secure databases that will store de-identified data. Only trained research personnel will have access to these files. Noom will have access to subjects' PHI including name, contact info, and demographics. However, Mount Sinai IT security has assessed the risk of potential PHI loss through previous similar work with Noom (IRB-16-01047).

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To test the comparative efficacy of Noom Health vs. Noom Digital Health for weight loss, quality of life, psychosocial functioning, and self-reported health status.	We will conduct remote scheduled direct entry interview and self-report questionnaire data at 8 time points (Screening/Baseline, 1 month, 4 months, 6 months, 12 months, 18 months, 24 months, and 30	Hypothesis 1: Noom Health users will show 6 month efficacy relative to Noom Digital Health for weight loss at post-intervention. Hypothesis 2: Noom Health users will show long-term (12 Month) efficacy relative to Noom Digital Health.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	months). Weight data will be collected by video observed scale. Digital scales will be provided for those who do not have access.	
Secondary		
To compare potential moderators of treatment response in Noom Health vs. Digital Health subjects.	We will conduct remote scheduled direct entry interview and self-report questionnaire data at 8 time points (Screening/Baseline, 1 month, 4 months, 6 months, 12 months, 18 months, 24 months, and 30 months). Weight data will be collected by video observed scale. Digital scales will be provided for those who do not have access.	Hypothesis 1: Clinical Profile (composite moderator) will show significant interaction with treatment condition, demonstrating that individuals with a more severe profile (older, less support, more health conditions, more psychosocial problems) will benefit more from Noom Health than Digital Control. Hypothesis 2: Weight suppression (absolute difference between highest and current weight) will moderate efficacy of Noom Health vs. Digital Education.
Tertiary/Exploratory		
To identify within treatment mechanisms of change among Noom Health group.		Hypothesis 1: Time series Bayesian belief network model of adherence will predict (a) study dropout, (b) successful weight loss, (c) quality of life. Hypothesis 2: Regular eating will mediate treatment effects of weight loss over time. Hypothesis 3: Self-efficacy of weight loss will mediate Noom Health vs. Noom Digital Health effects at post treatment and 12 month follow-up.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The study will: (a) test the Noom app in coach led groups with individuals interested in weight loss to determine if it significantly improves weight loss, quality of life, psychosocial functioning, and self-reported health status compared to a control.

We will use a randomized-controlled design comparing the Noom app administered in groups (6 months) to Digital Control with 6 months active maintenance in both groups. The proposal allows for a critical test of effect of Noom on relevant outcomes in the population.

All participants will complete a brief survey indicating that they would like to be contacted and includes a study description and availability. Then they will complete informed consent via a HIPAA-compliant videoconference (Zoom) and questionnaires on REDCap. Eligible participants will be randomized to one of two groups for 6 months intervention and 6 months maintenance (12 months of intervention): (1) Noom app with coaching (Noom Health; n=300), or (2) Digital Control (Noom Digital Health; n=300). We anticipate screening 684 subject to reach our recruitment goal of 600.

Participants' procedures:

- screening survey to determine eligibility and Baseline/Pre-intervention Zoom call
- Assessments: 24 hour recall interview, EDE-Q, Q-LES-Q-SF, IPAQ, Brief Self-Efficacy Scale for Healthy Eating, DASS, SF-36, PROMIS, Demographics and Smartphone Comfort

Intervention:

Noom Health participants will use Noom for 6 months of intervention and 6 months of maintenance (12 months total). Participants will use the app multiple times per day to log eating episodes (the number of episodes will vary by person). The features include diet, physical activity, and weight tracking, a social media group in the app, access to coaches, and personalized coach feedback. Coaches will interact with participants directly through the app. Participants will be encouraged to use the app for 6 months after intervention to maintain weight loss, with goal to maintain weight.

Noom Digital Health participants will use a limited version of Noom for 6 months of intervention and 6 months of maintenance (12 months total). The features include diet, physical activity, and weight tracking. Weight loss advice will be given once a week. Participants will use the app multiple times per day to log eating episodes (the number of episodes will vary by person). the app for 6 months after intervention to maintain weight loss, with goal to maintain weight.

Acceptability/Satisfaction assessments: During the intervention, we will send a 7-point Likert-type scale at monthly intervals Noom Health participants to assess satisfaction with the Noom app. For those in the Noom Digital Health condition, we will give a one question assessment at the same time points to indicate participants are still enrolled in research procedures.

Follow-up visits (1 month, 4 months, 6 months, 12 months, 18 months, 24 months, and 30 months): 24-hour dietary recall interview, EDE-Q, Q-LES-Q-SF, IPAQ, Brief Self-Efficacy Scale for Healthy Eating, DASS, SF-36, PROMIS, Demographics and Smartphone Comfort.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We are using a parallel randomized controlled design with 12 month follow-up to determine the efficacy and short-term durability of the effects of Noom on weight and associated changes in psychosocial and health. We chose an active control condition (Noom Digital Health) to control for proactive engagement in health related dietary and physical activity changes. These efforts are driven by expert information and

our control condition provides this expert information, consistent with CDC guidelines for healthy lifestyle. It is designed to reflect readily available expert information on weight loss and management in the community and adapted into a digital format to control for delivery method.

4.3 JUSTIFICATION FOR INTERVENTION

Commercial and medical weight loss interventions typically vary from 3-6 months with maximal weight loss achieved for the majority of participants within the first 3-4 months and rarely reaching maximal weight loss after 6 months of active intervention. Maintenance is an active process and requires a different set of skills and practices, so the Noom intervention builds on these behavioral weight loss and lifestyle intervention data to utilize expert coaching to increase uptake and contextualization of these skills in the individual's natural environment through coaching led smartphone assisted behavioral interventions targeting diet, exercise, and lifestyle. Observational data support 5-10% weight loss from the Noom app with adherence moderating this effect to a moderate degree. Consequently, Noom offers a digital adaptation of existing and well established behavioral weight loss interventions and maximized the windows of time for weight loss and maintenance based on these data.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment, 6 months intervention, 6 months active maintenance and the 1-month, 4-month, 6-month, 12-month, 18-month, 24-month, and 30-month follow-up assessments.

The end of the study is defined as completion of the 30-month follow-up assessment shown in the Schedule of Activities (SoA), **Section 1.3**.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

- Interested in the Noom platform
- BMI > 27 kg/m^2
- Between the ages of 18 and 60 at entry to the study
- Speak English

5.2 EXCLUSION CRITERIA

- Contraindication to smartphone use (e.g., seizures from prior smartphone use, do not own a smartphone).

- Acute suicide risk
- Pregnancy
- Current and planned breastfeeding*

Individuals who are pregnant should not participate in a medically unsupervised weight loss program due to the risks associated.

* Added after recruitment closed

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants may be asked to make significant changes to their lifestyle in relation to food intake and physical activity as recommended by the Noom coaches.

5.4 SCREEN FAILURES

Formal withdrawal, removal of the Noom app, or failure to complete scheduled measures will constitute drop-out for the study.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants will be recruited from Noom and from the Center for Excellence for Eating and Weight Disorders Program (EWDP) at the Icahn School of Medicine at Mount Sinai

Noom. Participants will have signed up with Noom directly to hear about research studies or have viewed the ad on the Noom app. These ads will contain a recruitment link to direct the participants to the research team.

EWDP. Patients or providers calling the Center for Excellence for Eating and Weight Disorders Program (EWDP) at the Icahn School of Medicine at Mount Sinai requesting information about research options for weight loss treatment will be emailed the recruitment link. A description will be provided as well.

Link. Upon clicking the recruitment link, participants will be directed to a 5-minute REDCap survey. The first page of the survey will include a description of the study. The second page will include 3 questions which will help with the booking process of the Zoom consent.

PPHS Guidance. This recruitment process aligns with the PPHS guidance > Screening Guidelines > Section 1, page 1, indicating that basic screening can take place prior to informed consent if it's part of the recruitment process. By incorporating this initial eligibility survey before the informed consent, we reduce burden for participants who are not eligible by lessening

the contacts with them to book a Zoom call, and by not conducting the 30-45 minute Zoom call. Additionally, we minimize risk to them by not collecting any identifiers other than email. By following PPHS guidance > Screening Guidelines > Section III, page 1, we adhere to consent process by having two different consent forms, one for screening and one for the full research study. This process will allow us to follow the HIPAA guidelines indicating that we should only collect as minimal information as possible.

Compensation will be $35 for the first assessment and $20 for each additional assessment. Additionally, in an effort to maintain retention, a lottery drawing will take place every 3 months for $50. Participants who win the lottery and also provided weight at their last follow-up will receive $100. For participants who are willing provide a social security number, they will be paid in the form of a check, otherwise it will be in the form of an Amazon gift card. The drawing will be done by the project manager in the EWDP office and the winner of the drawing will be notified by email. The winner will be chosen using random number generator *https://g.co/kgs/J8o9Hy*. The ID numbers of all participants still enrolled will be listed in an excel spreadsheet. In the number generator, a min and max number is entered. For this drawing, the min number entered will be "1" and the max will be the total number (count) of participants who are still enrolled. The number that appears will represent the row in the excel file and will determine the selected winner of that drawing. A purchase is not required for participants to be placed in the drawing. We are using a lottery to incentivize weight because it poses additional time and practical constraints for participants to complete. Because this commitment can vary randomly depending on where in weight loss journey, environmental changes (scale no longer at home, uses gym scale), or timing (assessment scheduled for mid-day when scale not accessible), the lottery offers incentive for those unpredictable extra time-burdens that our participants have reported in the first year of the study.

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

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

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

As approved in the prior Ideate protocol, participants will be randomized to one of the groups for 6 months intervention and 6 months maintenance: (1) Noom app with coaching, administered in a group format (Noom Health; n=300), or (2) Noom Digital Health (n=300).

6.1.2 ADMINISTRATION AND/OR DOSING

All participants will use their assigned app for 6 months of intervention and 6 months of maintenance (12 months total). Subjects will use the app multiple times per day to log eating episodes (the number of

episodes will vary by person). Participants will be encouraged to use the app for 6 months after intervention to maintain weight loss, with goal to maintain weight.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Noom Coaches will be trained to monitor the safety of their participants. Additionally, in the introductory material given to all participants, information about how to identify and report a crisis will be outlined. This is to safeguard participants in the event there is a problem with the facilitator. Since this is a non-clinical population (obese individuals without serious psychopathology) and Noom has never had any incidents with their typical overweight population, we do not anticipate this will be a problem. In the event a Coach discovers one of their group members has a serious psychiatric condition (e.g., severe eating disorder, substance dependence), he/she will be instructed to alert Noom and Mt. Sinai immediately via a shared e-mail address (e.g., sinai@noom.com). These incidents will be dealt with on a case-by-case basis and the absolute minimal course of action will be to contact the identified participant with relevant psychoeducational material and/or information about where they can go to receive help.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

As indicated in the approved Ideate protocol, we will use a randomized-controlled design. Participants will not be blinded to condition.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Both local and global adherence will be measured. Local adherence will be the percent of completed versus expected activities in each of the available categories (i.e., ((# completed/# expected) x 100%)), including: self-monitoring, activity levels, reading psychoeducational materials, problem solving, etc.). Global adherence will be measured with a similar calculation for virtual attendance/contact with scheduled coach check-ins.

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE THERAPY

N/A

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

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All participants will be contacted to complete all follow-up assessments unless they indicate that they would like to be withdrawn from the study. Participants are instructed in the consent form to contact the research staff directly if they would like to withdraw. Participants may indicate that they would like to withdraw from the intervention, but are still willing to complete future follow-up assessments. Contacts made to these participants will be assessment-related and not intervention-related. Depending on when the participant withdraws and under which circumstances would dictate the remaining procedures that they complete. Research staff will attempt to collect the reason for discontinuing at the time of withdrawal.

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 a participant from the study for the following reasons:

- The study is being stopped
- Significant study intervention non-compliance
- Lost-to-follow up; unable to contact participant
- Any event, medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- Currently breastfeeding or pregnant (withdraw from intervention, but will still complete follow-up surveys)

Should someone report that they are breastfeeding or pregnant, we will stop the intervention (aka withdraw from intervention). They will not receive any further intervention content. We will still ask if they'd be willing to complete surveys until the end of their 2.5-year participation as this would pose no harm the mother or fetus.

The reason for participant discontinuation or withdrawal from the study will be recorded in the tracking form in REDCap. Participants who are randomized and subsequently withdraw or are discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

Participants will be considered lost to follow-up if they withdraw from the study by directly contacting our research team or if they don't complete the follow-up assessments. Participants will be contacted

throughout the assessment window via phone, email, and the family/friend contact. If no contact is made during the assessment window, they will be deemed lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Noom Coaches will be trained to monitor the safety of their participants. Additionally, in the introductory material given to all participants, information about how to identify and report a crisis will be outlined. This is to safeguard participants in the event there is a problem with the facilitator. Since this is a non-clinical population (obese individuals without serious psychopathology) and Noom has never had any incidents with their typical overweight population, we do not anticipate this will be a problem. In the event a Coach discovers one of their group members has a serious psychiatric condition (e.g., severe eating disorder, substance dependence), he/she will be instructed to alert Noom and Mt. Sinai immediately via a shared e-mail address (e.g., *sinai@noom.com*). These incidents will be dealt with on a case-by-case basis and the absolute minimal course of action will be to contact the identified participant with relevant psychoeducational material and/or information about where they can go to receive help.

Within the context of the present study, Serious Adverse Events (SAEs) include any serious decline of psychological functioning (e.g., suicidal ideation, plan, or action) that requires immediate psychiatric intervention (e.g., inpatient hospitalization). This may occur while participants are in the assessment of follow-up components of the study. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse experiences when, based on appropriate medical judgement of the study physician, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes in this definition. The judgement of whether a particular AE meets the above criteria for an SAE for the proposed study will be determined by the PI. It will also be the PI's responsibility to manage all SAEs and to make referrals for appropriate care as necessary.

8.2 SAFETY ASSESSMENTS

N/A. There are no formal safety assessments performed in this protocol. If an adverse event is reported to the research team, we will follow-up as needed depending on the severity of the event and relation to the study.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

The intervention in this trial is low risk and is not expected to result in adverse events. Expected risks they may occur include anxiety related to eating or change in weight status or emotional discomfort during assessments. An adverse event will be defined as any untoward medical occurrence related to the intervention.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

A serious adverse event in this project will be defined as an adverse event that occurs during participation that is unanticipated, related to the research, and serious in nature (seriousness as defined by hhs.gov -- https://www.hhs.gov/ohrp/sites/default/files/ohrp/policy/advevntguid.pdf)

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

Adverse events will be classified on the following categories by research staff. All events will be brought to the attention of the PI, who will also confirm 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

Adverse events will be assessed to determine relation to the intervention. Determinations will be made by research staff. All events will be brought to the attention of the PI, who will also confirm relation to study.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.

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

8.3.3.3 EXPECTEDNESS

Research staff will be responsible for determining whether an adverse event is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures. All events will be brought to the attention of the PI, who will also confirm expectedness.

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

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of research staff during the study.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate tracking form in REDCap. Information to be collected includes event description, time of onset, assessment of severity, relationship to study procedures, and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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

8.3.5 ADVERSE EVENT REPORTING

As described in the prior Ideate protocol, there is no DSMB required for this project. All adverse events will be brought to the attention of the project manager immediately. The PI will be made aware of events within 24 hours. The IRB will be notified of non-serious events at the time of annual renewal.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Serious adverse events will be brought to the attention of the project manager immediately. The PI will be made aware of events within 24 hours. The IRB will be notified of serious events within 2 business days and the funding agency will be notified of serious events within 5 business days.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

Participants reporting that they are pregnant will be withdrawn from the intervention, but may still complete the follow-up surveys.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

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

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.]

8.4.2 UNANTICIPATED PROBLEMS REPORTING

UPs that are serious adverse events will be reported as indicated in section 8.3.4. > 1.1.3 and any other UP will be reported to the IRB and the funding agency as indicated in section 8.3.4. > 1.1.2. The investigator will report unanticipated problems to the IRB and will include the following information:

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

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint(s):

Hypothesis 1: Noom Health users will show 6 month efficacy relative to Noom Digital Health for weight loss at post-intervention.

Hypothesis 2: Noom Health users will show long-term (12 Month) efficacy relative to Noom Digital Health.

- Secondary Endpoint(s):

Hypothesis 1: Clinical Profile (composite moderator) will show significant interaction with treatment condition, demonstrating that individuals with a more severe profile (older, less support, more health conditions, more psychosocial problems) will benefit more from Noom Health than Noom Digital Health.

Hypothesis 2: Weight suppression (absolute difference between highest and current weight) will moderate efficacy of Noom Health vs. Noom Digital Health.

9.2 SAMPLE SIZE DETERMINATION

Mt. Sinai will use piecewise latent growth curve models with treatment as primary indicator. Using Monte Carlo simulation studies with 10,000 draws and 6 time points and 2 growth processes, Mt. Sinai evaluated sample size needed to detect significant differences on each growth process (within treatment, post-treatment follow-up). Mt. Sinai also varied missing at random patterns of missing of data at 10%, 20% and 30% increasing linearly over each timepoint. The results indicate that with 30% missing data, mean difference in BMI change of 1 .2 (SD =4.5), Mt. Sinai is 85% powered to detect significant difference at 24 month follow-up with N = 600. The power increases substantially for within treatment BMI change .8 (SD =4.5), power = .942. For psychosocial outcomes, N=600 with same parameters indicated 82-90% power to find treatment effects at 24 months, assuming a .20 SD unit difference between groups. Within treatment, the same difference is powered 90-98%.

For Aim 2, Mt. Sinai assumed full information on all moderators and tested the interaction effect with a composite moderator profile of 12 indicators. The interaction between latent moderator (M) and treatment was powered at .93 and .85 with N=600, and 30% attrition for within treatment and follow-up.

For Aim 3 power analyses were based on a 13-item adherence measure adapted from the Noom Monitor (Binge Eating) study and assumes network efficiency of .75. Mt. Sinai would examine the relationship between network entropy and the outcomes, with statistical power for the regression prediction at 100% for each outcome. Mediation model of weekly regular eating is a time series mediation model and assumes latent measure of meal-snack adherence will mediate changes in weight. The calculation is based on effect size goal of .25, .5, and .75. The results of simulations suggest that power for the smallest effect size (.25) is approximately .80 with 10% missing data or less and moderate correlations between time and change in regular eating (.3) and moderate correlation between regular eating and weight outcome (.3).

9.3 POPULATIONS FOR ANALYSES

All analyses will be intent to treat (include all randomized participants). Sensitivity analyses will include examining sources of missing data and alternative parameter estimates under different assumptions of missing data (e.g., missing completely at random, missing at random, multipleimputation).

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

We are using a latent growth curve model (piecewise) to model separate change processes assumed during weight loss and post intervention. All models will be examined for goodness of fit, normality and linear (vs. Nonlinear) change. Best fit models will be interpreted for primary effects.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Primary weight and psychosocial/health endpoints will be analyzed using the same piecewise linear growth curve model. Validity of model will be examined via BIC, AIC, and RMSEA with the later below .05 used as threshold for moving to interpretation of the model. We will test simple linear models and build complexity (non-linear, robust model estimation) based on model fit and observation of outliers and potential subgroups. Missing data will be assumed missing at random during initial model estimation and sensitivity analyses using (missing completely at random) tests to evaluate the impact of missing data.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The same modeling approach will be used for secondary endpoints and moderator models will include first, estimation of latent factor based on demographic variability and the interaction of this latent variable and treatment estimated as formal hypothesis test.

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline variables (demographics and anthropometrics) will be compared at baseline using t-tests and chi-square to determine if pre-treatment bias exists in randomization.

9.4.6 PLANNED INTERIM ANALYSES

N/A—no interim analysis planned.

9.4.7 SUB-GROUP ANALYSES

Our moderator analyses rely on empirically derived profiles (as opposed to p-hacking search for group difference) to maximize likelihood of identifying meaningful differences between relevant individuals.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Data will be tabulated in person-period format.

9.4.9 EXPLORATORY ANALYSES

We will utilize repeated measures Bayesian belief network to establish adherence within the Noom group and examine its changes to relationship over time. BBNs are most often used to establish greatest

predictive value related to available data and tested against randomly sampled (80-20) develop and test data sets.

Our Mediation model of weekly regular eating is a time series mediation model and assumes latent measure of meal-snack adherence will mediate changes in weight and included a time-varying set of latent variables that change in parallel to our primary outcome.

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

SOP HRP-090 Informed Consent Process for Research is being used. Interested individuals will be sent a pdf of the consent form to review before reviewing it with study staff. Informed consent and screening interviews will be conducted via a HIPAA-compliant videoconference (Zoom). A member of the study staff will review the study protocol and obtain written informed consent using the full-study e-consent form. Voluntary written informed consent will be completed prior to completing study procedures in accordance with the PPHS of Mount Sinai. Our consent documents will be submitted with the protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Prior to the consent call, interested individuals will be sent a REDCap link to the electronic version of the full-study consent form. Informed consent and screening interviews will be conducted via a HIPAA-compliant videoconference (Zoom). A member of the study staff will review the study protocol and obtain written informed consent using the full-study e-consent form. Voluntary written informed consent will be completed prior to completing study procedures in accordance with the PPHS of Mount Sinai. The consent process includes a description of the remaining screening procedures and assessments, treatment, and other study requirements and will be obtained in a closed office with only members of the research group present. No reference to the potential subject's identity will be made outside of closed quarters. The consent form includes an explanation of study procedures, their time commitments, risks and benefits, alternatives to participation, the confidentiality of information, and the rights of research subject. Participants will be given the opportunity to have all their questions answered. Participants' understanding of the protocol will be examined by direct questioning prior to their signing the consent forms. The potential subject will provide their e- signature and name as well as the date of the consenting process on the e-consent form. After the subject submits the form, the study staff member obtaining the consent will provide their signature, name, and the consenting date on the signed e-consent form and send a copy of the form to the participant via an encrypted email. All study related questions from study

participants that a research staff member is unable to address will be referred to the Principal Investigator or other co-investigators. No further information will be gathered until participants have provided written, signed informed consent.
The consent form will explicitly notify participants that participation is voluntary, can be discontinued at any time and will not affect their medical care or status in the Mount Sinai Health System. Patients will be screened to ensure they do not meet criteria for exclusion.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

As approved in prior Ideate protocol, if the benefit-risk analysis of this study changes, based on the number of SAEs related to study procedures, we will consult with the IRB and determine how to proceed (e.g., changes to the inclusion criteria, additional criteria for discontinuation of research participation, ending the trial prematurely).

10.1.3 CONFIDENTIALITY AND PRIVACY

To protect confidentiality, the following precautions will be taken: (1) all questionnaire and interview data will use study identification numbers; (2) raw data will be kept in a locked file cabinet and will be available only to research staff; (3) electronically stored data will be coded and password protected in a secure database behind the Mount Sinai firewall.
The database containing participant data at Noom Inc. is hosted by Rackspace, and features a virtualized mySQL instance. These systems are accessible only via secured socket connections using 256-bit encryption, with a second layer of security to access the actual databases themselves. There is no protected health or identifiable information in the database, only a unique id. There is no public IP for the database. The database is managed, so that it is continually patched. It is on a closed VLAN, behind an industrial strength firewall. There is a pair of virtualized webservers behind a similar firewall, accepting the requests. Access is restricted to Artem Petakov, the designated database security officer for this study. The web server is similarly behind an industrial strength firewall, only accessible via SSL. Rackspace is one of the best providers in the industry, maintaining very high security standards, with policies in place to prevent unauthorized access to the systems.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Smartphone application data from each participant phone will be sent to the centralized secure database at Noom, Inc. that will solely contain data for study participants. The Noom application is HIPAA compliant, and all users will be provided with HIPAA Notice of Privacy Practices. The data will only be identified by a 128-Bit number randomly generated for each participant and data will only be code-based. One electronic copy linking participant names and individualized identifier codes will be stored in a password-protected document on a computer at Noom, Inc. The server system where the data is stored requires an authorization token to log into the system, and a second authorization token to access the database. Artem Petakov, the Noom, Inc. CTO, is the only person who has access to both tokens.
The proposed study data will be used only for research purposes. Only trained and qualified research team members will have access to study data. To further reduce possible risk to participants, all paper data will be will be stored in locked rooms and electronic data on password-protected systems. Participants will be assigned a study code, which is the only identifier that will be used when labeling study data. In addition to promoting participant confidentiality, the above measures will also facilitate data sharing with other investigators in the future.

The data will be stored for 7 years following data analysis/publication, as per Mount Sinai policy.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor or Independent Safety Monitor**
Thomas Hildebrandt, PsyD	*Name, degree, title*
Icahn School of Medicine at Mount Sinai	*Institution Name*
53-55 E 96th St. New York, NY 10029	*Address*
(212) 659-8673	*Phone Number*
tom.hildebrandt@mssm.edu	*Email*

A description of the Data Monitoring Committee has been submitted along with the protocol.

10.1.6 SAFETY OVERSIGHT

As indicated in the previously approved protocol, Thomas Hildebrandt will serve as the Principal Monitor. Study data will be reviewed by the investigative team on a monthly basis. Reporting or resolution of any discovered issues will be the responsibility of the study PI. A description of the Data Monitoring Committee has been submitted along with the protocol.

10.1.7 CLINICAL MONITORING

10.1.810.1.8 N/A

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

- Dr. Tom Hildebrandt will conduct all data safety monitoring on a monthly basis with the investigative team. As approved in the Ideate protocol, we will conduct monthly data audits to evaluate the quality of the data entered and to ensure missing data or data entry errors are avoided. This process involves reviewing individual case data, interview data, biometric data and laboratory data.
- As approved in our previous proposal, independent audits will not be conducted.

10.1.7
Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured on source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

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

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

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

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Source Records:

1. Measures of eating and activity:
a. 24 hour recall interview. Foods and beverages consumed during the 24-hour period before the assessment will be asked.
b. Eating Disorder Examination Questionnaire (EDE-Q). EDE-Q measures dietary restraint, eating, shape, and weight concerns, loss of control eating episodes.
c. International Physical Activity Questionnaire (IPAQ). The IPAQ is a brief self-report measure of time spent in an average week completing vigorous or moderate physical activity, walking, and sitting.
2. Measures of Related Symptoms:
a. Depression Anxiety Stress Scales (DASS). The DASS is a 42-item self-report measure of negative emotional states with subscales of depression, anxiety, and stress symptoms.
b. Short Form-36 Health Survey (SF-36). The SF-36 is a 31-item self-report of health-related quality of life measure that generates two scores: The Mental Composite Score (MCS), and the Physical Composite Score (PCS).
c. Brief Self-Efficacy Scale for Healthy Eating. The Brief Self-Efficacy Scale for Healthy Eating is a 12-item self-report of self-efficacy with scales specific to physical activity, healthful eating and weight-loss.

d. PROMIS Sleep-Related Impairment is a self-report questionnaire that assesses sleep impairment over the last 7 days. The measure consists of 16 individual items and takes 2-5 minutes to complete.
e. The Quality of Life, Enjoyment, and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) is a 16 self-report assessment of overall enjoyment and satisfaction with physical health, mood, work, household and leisure activities, social and family relationships, daily functioning, sexual desire/interest/performance, economic status, vision, ability to get around physically, overall well-being, medications, and contentment.

3. Noom App Data:

a. Adherence: Both local and global adherence will be measured. Local adherence will be the percent of completed versus expected activities in each of the available categories (i.e., ((# completed/# expected) x 100%)), including: self-monitoring, activity levels, reading psychoeducational materials, problem solving, etc.). Global adherence will be measured with a similar calculation for virtual attendance/contact with scheduled coach check-ins.
b. Attrition: Formal withdrawal, removal of the Noom app, or failure to complete schedules measures will constitute drop-out for the study.
c. Compatibility: We will capture and categorize the type of problems encountered by in the course of the trial and their 'fixes' for individual's phones. Percentage of successful fixes will be our compatibility measure.
d. Anthropometric Data: Participants will complete a measure of height and weight. As this information will be collected remotely, participants will be asked to use a secure Zoom meeting to complete the weight with a member of the research team viewing the scale.

Smartphone application data from each participant phone will be sent to the centralized secure database at Noom, Inc. that will solely contain data for study participants. The Noom application is HIPAA compliant, and all users will be provided with HIPAA Notice of Privacy Practices. The data will only be identified by a 128-Bit number randomly generated for each participant and data will only be code-based. One electronic copy linking participant names and individualized identifier codes will be stored in a password-protected document on a computer at Noom, Inc. The server system where the data is stored requires an authorization token to log into the system, and a second authorization token to access the database. Artem Petakov, the Noom, Inc. CTO, is the only person who has access to both tokens.

The proposed study data will be used only for research purposes. Only trained and qualified research team members will have access to study data. To further reduce possible risk to participants, all paper data will be will be stored in locked rooms and electronic data on password-protected systems. Participants will be assigned a study code, which is the only identifier that will be used when labeling study data. In addition to promoting participant confidentiality, the above measures will also facilitate data sharing with other investigators in the future.

10.1.9.2 STUDY RECORDS RETENTION

The data will be stored for 7 years following data analysis/publication, as per Mount Sinai policy.

10.1.10 PROTOCOL DEVIATIONS

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported to Noom, Inc Dr. Andreas Michaledels. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing

and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.]

10.1.11 PUBLICATION AND DATA SHARING POLICY

This data will be made available through permission from Noom, Inc. All publication material will be managed by the investigative team and in accordance with contract.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the Noom, Inc and conflict of interest office at Mount Sinai has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration

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

10.4 PROTOCOL AMENDMENT HISTORY

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

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

Include a list of relevant literature and citations for all publications referenced in the text of the protocol. Use a consistent, standard, modern format, which might be dependent upon the required format for the anticipated journal for publication (e.g., N Engl J Med, JAMA, etc.). The preferred format is International Committee of Medical Journal Editors (ICMJE).

Examples:

- ***Journal citation***
  Veronesi U, Maisonneuve P, Decensi A. Tamoxifen: an enduring star. J Natl Cancer Inst. 2007 Feb 21;99(4):258-60.
- ***Whole book citation***
  Belitz HD, Grosch W, Schieberle P. Food chemistry. 3rd rev. ed. Burghagen MM, translator. Berlin: Springer; 2004. 1070 p.
- ***Chapter in a book citation***
  Riffenburgh RH. Statistics in medicine. 2nd ed. Amsterdam (Netherlands): Elsevier Academic Press; c2006. Chapter 24, Regression and correlation methods; p. 447-86.
- ***Web Site citation***
  Complementary/Integrative Medicine [Internet]. Houston: University of Texas, M.D. Anderson Cancer Center; c2007 [cited 2007 Feb 21]. Available from: http://www.manderson.org/departments/CIMER/.
- ***Electronic Mail citation***
  Backus, Joyce. Physician Internet search behavior: detailed study [Internet]. Message to: Karen Patrias. 2007 Mar 27 [cited 2007 Mar 28]. [2 paragraphs]
- ***References to package insert, device labeling or investigational brochure***
  Cite date accessed, version number, and source of product information.