Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

Supplement 1 – Study Protocol

PROTOCOL TITLE:
SMART Weight Loss Management

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Clinical Trials Registration Number: NCT02997943

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1.0 Purpose of the study:

Obesity's high prevalence and costs make it a public health crisis, but current standard of care treatment impedes uptake and depletes resources by taking a one-size-fits-all approach. Guidelines recommend provision of expensive, burdensome treatment components (e.g., counseling, meal replacement) continuously to all consumers regardless of weight loss response. Stepped care that tries less costly evidence-based treatments first, reserving more resource- intensive treatments for suboptimal responders is a logical, equitable population health management strategy. However, stepped care approaches to obesity treatment have not yet incorporated inexpensive, widely available mHealth tools. It is unclear whether conjoint clinical and cost outcomes are better optimized by providing a low cost, low intensity, autonomously controlled mHealth treatment as the initial treatment with risk of nonresponse, or by providing a more costly, traditional obesity treatment with the potential to create a dependency that undermines autonomous motivation. The potential pitfall of beginning with mHealth treatment is that long-term outcome may be poor if nonresponse to initially insufficient treatment allows demoralization to set in. To reduce that risk, we will identify nonresponders earlier than previously has been possible by applying a predictive model derived from our prior mHealth obesity research and will quickly reallocate nonresponders to augmented treatment. We propose to use a novel experimental approach, the SMART (Sequential Multiple Assignment Randomized Trial), to randomize 400 overweight/obese adults to one of two first line treatments, either (1) a wireless feedback system (WFS), or (2) the WFS plus coaching (WFS +C). Those who do not respond to the first line treatment (i.e., evidenced by failure to lose weight) will be re-randomized to one of two subsequent augmentation tactics, either: (1) Modestly Step-Up: add another mHealth component (e.g., text messages), or (2) Vigorously Step-Up: add both a mHealth component (e.g., texts) and a more traditional component (e.g., coaching, meal replacement).

Responders will continue with the same first line treatment for 12 weeks. Assessments will occur at 3, 6, and 12 months to determine (1) whether mHealth or traditional obesity treatment (coaching) is the optimal first line treatment for overweight/obese adults; and (2) whether the optimal response to weight loss failure is to modestly or vigorously augment the first line treatment. As the first stepped care trial to integrate mHealth tools and implement our predictive model of weight loss failure, SMART will be the most temporally and resource efficient strategy evaluated to date.

Specific Aims

Primary Aim Optimal first line treatment. To determine whether the optimal first line treatment for a population of overweight and obese adults is mHealth alone (WFS) versus mHealth plus coaching (WFS+C). Although WFS+C provides greater and more resource-intensive social support, providing WFS alone as the initial treatment supports self-determination by anchoring participants on the frame that weight regulation is autonomously guided behavior. Therefore, we hypothesize that providing WFS alone as initial treatment will be noninferior to initial treatment with WFS+C in its effects on weight loss.

Secondary Aim Optimal augmentation tactic to address treatment nonresponse. To determine whether the optimal response to early weight loss treatment failure is to modestly augment the first line treatment with another inexpensive mHealth component (messaging) or to vigorously augment with both messaging and a more traditional component (coaching or meal replacement). We hypothesize that vigorous augmentation will produce greater weight loss than modest augmentation.

Tertiary (Exploratory) Aims

Moderators and Mediators. To identify baseline demographic variables (sex, age, SES, race and ethnicity) that moderate treatment effects and to examine whether between-treatment differences in 6-month weight loss are mediated by self-efficacy, autonomous motivation, and extent of self- monitoring.

Maintenance. To examine whether end-of-treatment (3 month) differences between WFS versus WFS+C are maintained at 6- and 12-month follow-up.

Best treatment sequence. To find the optimal sequence of treatment tactics by comparing effects on 6 month weight loss and cost-effectiveness (cost/pound lost) of the four treatment sequences embedded in the SMART design.

Outcomes

The pre-specified primary outcome was between-group difference in 6-month weight change. Proportion of participants who achieved 5% weight loss at 6 months, the patient's treatment goal and a clinically important outcome, was pre-specified as exploratory. Pre-specified secondary outcome were between-group differences in weight change at 3- and 12-month follow-ups, and weight change difference at 6 months among participants with initial non-response who received modest versus vigorous treatment augmentation. Pre-specified exploratory outcomes were weight change differences at 3 and 12 months by nonresponders who received modest versus vigorous step-ups of initial treatments, and weight change difference at all follow-ups by treatment sequence and demographic characteristics.

2.0 Background / Literature Review / Rationale for the study:

The proposed project seeks to develop an effective, resource-sensitive strategy to manage weight loss treatment for a heterogeneous population of overweight/obese adults. Most traditional, efficacious weight loss interventions[1-4] are limited in terms of scalability and cost effectiveness. Stepped care that begins with less costly evidence-based treatments,[5,6] reserving more resource- intensive treatments for suboptimal responders[7-9] is a logical, equitable population health management strategy. To-date, mHealth tools have not been tested as the initial component of stepped obesity treatment. Introducing mHealth tools at an early treatment stage may reduce costs by decreasing the odds that some patients receive unnecessary care.[10,11]

Current gaps in knowledge are: (a) whether the obesity treatment sequence should start with a mHealth component alone, or include traditional support in the form of coaching; (b) whether the augmentation tactic for treating non-responders who fail to lose weight in response to first line treatment should be to add another mHealth component, or an mHealth component plus a traditional treatment component; and (c) who benefits from mHealth components alone versus needing traditional treatment components.

To address these gaps we will utilize a novel experimental approach, the SMART (Sequential Multiple Assignment Randomized Trial).[12-14] Participants will be randomized to one of two first line treatments: wireless feedback system alone (WFS), or WFS plus coaching (WFS+C). Non-responders will be re-randomized after two weeks to one of two augmentation tactics: Modestly Step Up by adding a mHealth component, or Vigorously Step Up by adding a mHealth component and a traditional component. Responders will continue with the same first line treatment for 12 weeks.

3.0 Inclusion and Exclusion Criteria:

Individuals meeting the following eligibility criteria will be considered for participation:

Eligibility Criteria

Participants will be adults between ages 18 and 60 with BMI between ≥27 - 45 kg/m2 and <350 lbs; weight stable (no loss or gain >25 lbs. for the past 6 months); interested in losing weight and not enrolled in a formal weight loss program; not taking weight loss medications or supplements that may

cause weight change; not using meal replacements or willing to stop using them. Eligible participants will own a Smartphone (Android or iOS), will be willing to install the SMART App, and will voluntarily provide informed consent. Participants must also plan to reside in the Chicagoland area for the duration of their participation (i.e., 12 months) and maintain at home wi-fi internet for at least the first 6 months of their participation. Participants who have participated in our previous studies (participants who fill out the webscreen are checked against our previous study records) must wait three months before entering SMART in addition to meeting the other study criteria.

Exclusion Criteria

For safety, participants with unstable medical conditions (uncontrolled hypertension, diabetes - uncontrolled or treated with insulin, uncontrolled hypothyroidism, unstable angina pectoris, transient ischemic attack, cancer undergoing active treatment, or cerebrovascular accident or myocardial infarction within the past six months, Crohn's disease), pregnancy, lactation or intended pregnancy, active suicidal ideation, anorexia, bulimia, binge eating disorder, requiring an assistive device for mobility, or those with any current condition that may limit or prevent participation in moderate activity will be excluded. Those with current substance abuse or dependence besides nicotine dependence will be excluded. Because the Fitbit Aria wireless scale relies on bioimpedance analysis, individuals with a pacemaker or other electrical implanted device will be excluded from the study.

Individuals will also be excluded if they are currently participating in one of our weight loss studies (we check participants who fill out the webscreen against previous study records), are identified as individuals who did not complete or adhere to a previous study protocol, have ever had bariatriac (or LapBand surgery), are considering or currently on a wait-list for bariatric or LapBand surgery, or determined to be unlikely to be able or willing to complete study procedures based on conversations during the phone screen, pre-randomization call or baseline assessment. In order to prevent potential contamination of conditions and results, participants who live together will not both be allowed to enroll in the study. We will cross-check and flag duplicate addresses and phone numbers as potential participants complete the online webscreener. During the Orientation session, we will discuss this exclusion criteria with potential participants. Only one person from each household may enroll in the study, concurrently or otherwise.

Special Populations

The following populations will not be included in this study:

1. Adults unable to voluntarily provide consent will not be included in this study.
2. Individuals who are not yet adults (minors): infants, children, teenagers will not be included in this study.
3. Prisoners or other detained individuals will not be included in this study.
4. Pregnant women will not be included in this study.

4.0 Sample Size:

A total sample size of 400 overweight and obese adults will be recruited to participate in this study.

Research Locations:
Study orientation, randomization session, tech training, and in-person assessments (i.e., baseline, 3 month, 6 month, and 12 month sessions) will take place in the Department of Preventive Medicine at Northwestern University's Chicago Campus. During the intervention phase, participants will engage with intervention components remotely.

5.0 Multiple sites:

Northwestern University will be the lead site for this study. All study visits and participant interactions will take place at the Northwestern Chicago campus. The University of Michigan will also be involved in the study as an external site, primarily through interactions with Dr. Inbal Nahum-Shani. Dr. Nahum-Shani will be responsible for oversight of the recruitment, enrollment, and random assignment designs of the study, and will be involved in data analysis as well as interpretation and preparation of manuscripts and presentations. While engaged in the research process, Dr. Nahum-Shani will not be involved in the collection of the research material, and will not have access to any identifying participant data or information. Any data sharing for analysis purposes will be protected and de-identified, as described in section 16.0.

A bi-weekly progress meeting will take place between the principle investigators of each site, Dr. Spring and Dr. Nahum-Shani, to ensure successful coordination of activities among the sites. This will be an opportunity to confirm that each site is complying with the study protocol, to communicate any changes in the study procedures, and to ensure each site is aware of any problems, interim results, or other important information pertinent to the study. The project coordinator will also attend these meetings.

The principle investigator of the external site, Dr. Inbal Nahum-Shani, will ensure that University of Michigan research personnel involved in the study are appropriately qualified and meet its institutional standards for eligibility to conduct research. They will also ensure that their research activities are in compliance with the IRB's determinations. Any non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.
All required approvals for multiple site research have already been obtained for this study.

6.0 Reliance Agreements/Single IRB:

The Northwestern IRB will be the IRB of record for this study. The oversight responsibility of the Northwestern IRB, and the University of Michigan's reliance on Northwestern for continuing oversight of the human subject research in the SMART study, is documented in an IAA.

7.0 Procedures Involved:

Study Design

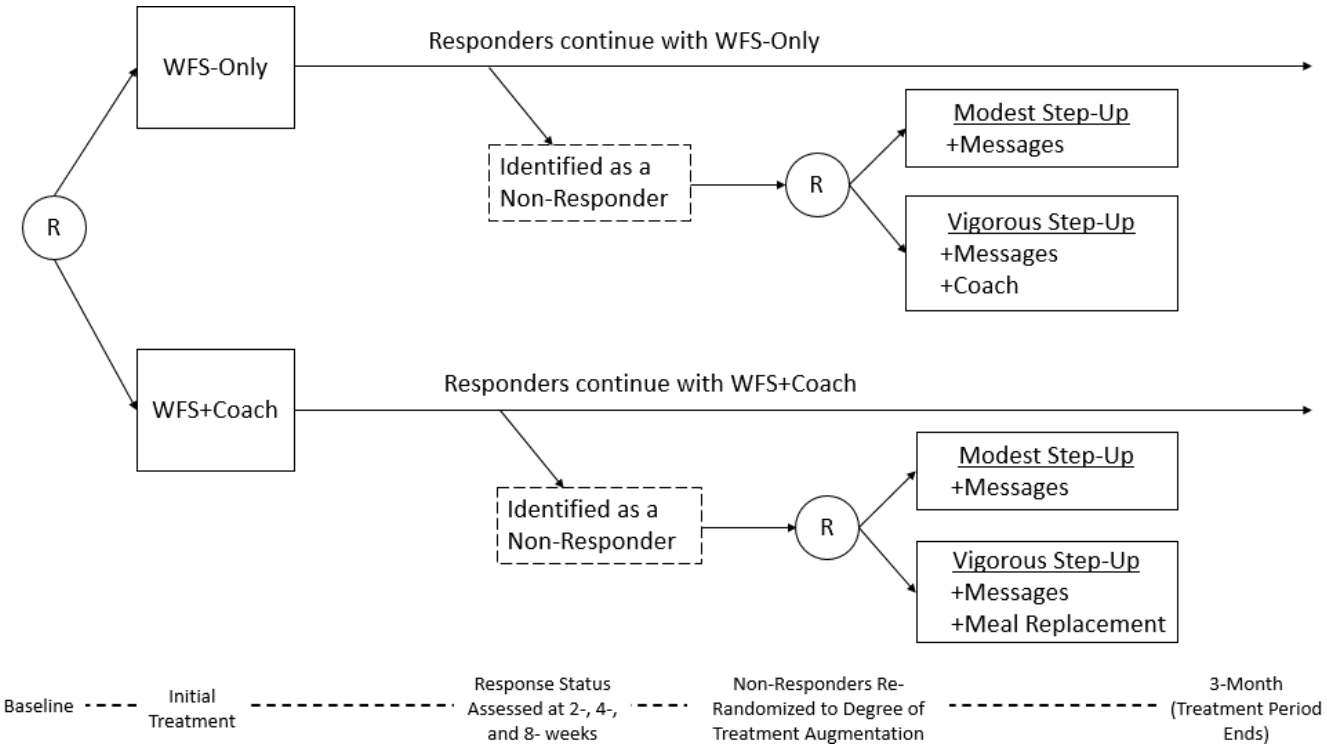
The proposed project will utilize the Sequential Multiple Assignment Randomized Trial (SMART; Figure 1) study design. All eligible participants will initially be randomized to one of two first line treatments: (1) WFS (WFS); or (2) WFS plus 12 weekly coaching calls (WFS+C). Participants will be notified of their initial treatment assignment during an in-person baseline assessment/randomization session. All participants will download the SMART App, and receive training on all tech components: 1) The SMART App, 2) loaned wireless accelerometer (e.g., Fitbit Zip), 3) loaned wireless scale (e.g., Fitbit Aria). Participants will be trained to self-weigh daily using the Fitbit Aria wireless scale.

Design of a Sequential Multiple Assignment Randomized Controlled Trial to Optimize Weight Loss Management.

In Figure 1 (below) Stage 1 randomization (R) to WFS versus WFS+C tests which first line treatment maximizes weight loss. Stage 2 re-randomization of nonresponders (those who achieve < 0.23 kg weight loss per week) tests whether modest (low resource-intensive) augmentation with technology (messaging) versus vigorous augmentation with a more resource-intensive traditional weight loss treatment component (coaching or meal replacement) maximizes 6-month weight loss.

Non-response at either week 2, 4, or 8 triggers one Stage 2 re-randomization. Note that messaging is used as the modest augmentation for nonresponders to either initial treatment because neither group has responded well to their initial treatment; messaging uses few resources, and neither group has previously received it. In contrast, the Vigorous Step-Up differs depending upon the initial treatment because one first line treatment group, but not the other, has already received a resource-intensive traditional weight loss component (coaching) as initial treatment. For that group, coaching continues, rather than representing a treatment augmentation.

Figure 1



Non-response (failure to lose at least 0.5 lb/week on average) will be assessed at the beginning of weeks 2, 4, and 8 (weight recorded Sunday, Monday or Tuesday). Assessing non-response at the beginning of week 2 is based on preliminary data analysis from the ENGAGED study indicating that weight loss of less than 1 lb. by the end of week 2 is highly predictive of treatment failure (i.e., losing less than 5% at month 6). Additional assessments of non-response at the beginning of weeks 4 and 8 are based on recent evidence indicating that 1 and 2 month weight losses of at least 0.5 lb/week predicts 1 and 8 year weight changes.[15,16] Based on data from the ENGAGED study and prior studies,[17] we expect that *by the end of week 8/beginning of week 9 approximately 50% of study participants will be classified as non-responders*. Non- responders will be notified of the subsequent treatment assignment. Participants will be classified as responders if they do not meet the criterion for non-response (i.e., lose an average of at least 0.5 lb/week). Responders will continue with the first line treatment.

The first time a participant is classified as a non-responder, he/she will be re-randomized to one of two ***augmentation tactics***: (1) Modestly Step-Up, or (2) Vigorously Step-Up. Specifically, Modestly Step-Up captures a tactical decision to modestly augment the initial treatment with one mHealth treatment component that was not offered initially. We operationalize this tactic by adding messages (push notifications) to the initial treatment (either to WFS alone or WFS+C). Vigorously Step- Up captures a tactical decision to vigorously augment the initial treatment with one mHealth component and one traditional treatment component that was not offered initially. For non- responders who received WFS alone initially, we operationalize this tactic by adding messaging and coaching; whereas for those who started with WFS and coaching, we operationalize this tactic by adding messaging and meal replacement (because coaching was already offered as part of the initial treatment). We opted to vigorously augment WFS alone with messaging and coaching; rather than with messaging + coaching + meal replacement because the latter operationalization would add two traditional components to the initial treatment rather than one. That would constitute a very

ered initially. According to self-determination and competence motivation theory[18,19] people have an innate need to act with a sense of choice and agency, developing a self-concept of competence based on their own personal experiences of mastery. Offering too vigorous augmentation risks exceeding the "support threshold," the point at which one can still attribute accomplishments to personal effort and competencies.[20,21] Providing an excessive increment in support can tacitly undermine an individual's motivation, implying that he/she lacks competence and needs a great deal of remedial support.

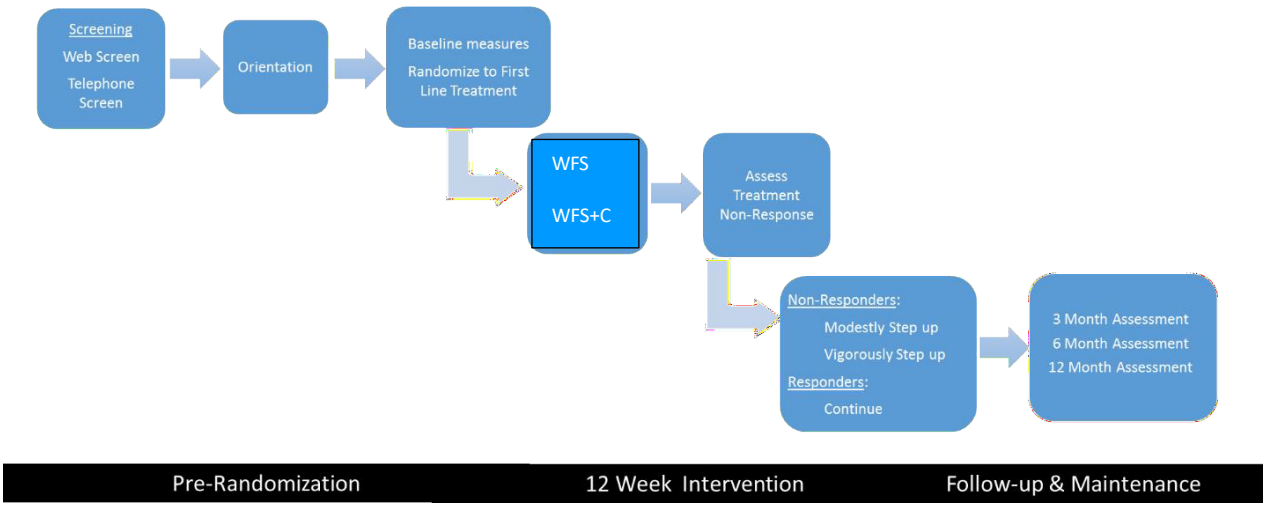
Although Vigorous Step-Up is operationalized differently depending on the initial treatment offered to non-responders, cells A and D in Figure 1 represent the same tactical decision, namely to vigorously augment the initial treatment for non-responders.[13,22,23] Similar approaches have been implemented in other SMART studies (http://methodology.psu.edu/ra/smart/projects).

Figure 1 is a factorial design. Hence, as described in the analytic plan below, no single cell (A-F) will be compared to another single cell.[22] Randomization, stratified by sex, baseline BMI and weight loss, will be computer-generated using a minimization allocation method.[24,25] This procedure will ensure that treatment groups are balanced for variables that may correlate highly with longitudinal outcomes. Specifically, the first randomization will be stratified by gender and baseline BMI (BMI > 35 vs BMI ≤ 35), and the second randomization will be stratified by weight loss (weight loss > 0 vs. weight loss ≤ 0).

Study Procedures

The sequence of study activities is presented in figure 3.

Figure 2: SMART Study Sequence



Web Screening (10 minutes)
Recruitment materials will direct interested individuals to the SMART study website. The website will provide interested candidates with a brief description of the study and eligibility criteria. A link to the web screen (REDCap) will be posted on the SMART website. Candidates will confirm interest in research participation, provide contact information and scheduling availability, and complete screening questions assessing for eligibility criteria (e.g., demographics, weight, BMI). If the study is experiencing a high volume of participants and is

nearing capacity, eligible candidates will receive an email notifying them that we will reach out in the near future to schedule their phone screen. When the study has room, eligible candidates will be contacted by study staff for a telephone interview. We will attempt to reach potential participants up to three times by phone; if we are unable to reach potential participants by phone to complete the telephone screen, we will make one final email attempt. Those who are not eligible will receive an email from the study staff informing them of ineligibility and providing other weight loss resources.

Telephone Screening (15 minutes)
During the telephone screening call, candidates will be verbally informed about the screening procedures, and study staff will explain the research and ask about the candidate's interest in participating. Staff will screen for inclusion and exclusion criteria. Candidates who remain interested and eligible will be scheduled to attend an orientation session.

If eligible: Study staff will email an "Orientation Reminder", parking map, and copy of the IRB approved informed consent document to participants scheduled to attend the in- person Orientation session.

If not eligible: Those who are not eligible or not interested in participating will be offered other weight loss resources and opportunity to be contacted for future studies. Study staff will offer to send an email with a list of Chicago area weight loss resources.

Attempts to contact: Study staff will make up to three phone attempts and one final email attempt to reach candidates to complete the telephone screening. If unable to reach after the email attempt, study staff will mark the individual as "ineligible," with the reason as "unable to contact."

Group Orientation (1½ - 2 hours)
At orientation, staff will conduct an equipoise induction to discuss the pros and cons of each treatment condition (to reduce drop-out after randomization). Candidates who are eligible and interested in participating will provide informed consent and contact information and receive instructions to: 1) track food intake and physical activity, for a 7-day period; 2) identify two locator people; and 3) complete online baseline assessments. They will also be scheduled for their pre-randomization call.

Pre-Baseline Session At-Home Activities (2.5 hours)
Candidates may expect to spend 15 minutes/day completing the 7-day food and physical activity log. Candidates will spend an additional 30 minutes completing online baseline questionnaires.

Pre-Randomization Call (15 minutes)
Prior to the Pre-Randomization phone call, participants will have signed the informed consent, completed the online questionnaires, and filled out the food intake and physical activity diary for seven consecutive days. The locator surveys must also be completed by two emergency contacts. The Pre-Randomization call will be used to minimize withdrawal once participants have been randomized. Baseline Health Assessment appointments will be scheduled during call. Study staff will send a reminder email prior to the scheduled Health Assessment.

Baseline Health Assessment (30 minutes)
During the Baseline Health Assessment study staff will gather anthropometric data, administer questionnaires (see Study Measures), and confirm a candidate's eligibility to participate in the study. Those who complete the in-person baseline assessments and remain interested and eligible will be randomized and will move immediately into a Randomization and Tech Training Session.
Those who are determined to be ineligible during the Baseline Health Assessment will be offered information on Chicago-area weight loss resources.

Initial Randomization (30 minutes)
Randomization will be computer-generated using a minimization allocation method.[24,25] First line intervention strategy assignment (WFS or WFS+C) will be stratified by gender and baseline BMI. Re-randomization of nonresponders will be stratified by whether the participant has lost any weight since baseline. These procedure will ensure that treatment groups are balanced for variables that may correlate highly with longitudinal outcomes. Candidates who, when queried, indicate unwillingness to participate in any condition will not be randomized. Participants will be informed of their first line intervention assignment at the in-person Randomization session. Participants will spend approximately 30 minutes discussing their randomization condition and study components with a staff member.

Tech Training (50 minutes – 1-1/2 hours)
During the in-person Randomization, participants will be trained on all technology used during the study, including the SMART App, Aria wireless scale, and Fitbit Zip. Candidates will download the SMART App and receive training on how to self-monitor their diet and physical activity in the App. Study staff will instruct them on how to self-weigh daily on the Aria wireless scale. Training will emphasize weighing upon awakening, after urinating, with minimal or no clothing. Staff will demonstrate how to set up the wireless scale if the participant would like. Staff will also train participants how to set and change their wake time and bedtime. Staff will provide the participants with a Randomization Checklist to recap the details of the visit, and to remind them of the upcoming steps of the study. Study staff will also contact participants following Randomization/start-up to confirm all tech devices have been engaged and are working properly.

Augmentation Randomization
Randomization of intervention augmentation tactics will take place when a participant is identified as a non-responder (i.e., failure to lose weight). Non-response (failure to lose at least 0.5 lb/week on average) based on participant's at home self-weighing will be assessed at the beginning of weeks 2, 4, and 8 (weight recorded on Sunday, Monday or Tuesday of those weeks). Randomization of augmentation tactics will be stratified by weight loss (weight loss > 0 vs. weight loss ≤ 0). Participants in the WFS only group will either be randomized to receive messages (modestly step up) or messages and coaching (vigorously step up). Participants in the WFS + Coaching group will receive either messages (modestly step up) or messages and meal replacements (vigorously step up). Staff will contact non-responders, notify them of the subsequent treatment assignment, and review the changes to treatment. Participants will be classified as responders if they *do not meet* the criterion for non-response (i.e., lose an average of at least 0.5 lb/week). Responders will continue with the first line treatment, without augmentation, through week 12.

Online Questionnaires (20 minutes each)
Participants will be asked to complete online questionnaires prior to attending the follow-up health assessments. Online questionnaires will measure self-efficacy, autonomous motivation, and health related quality of life. Participants may expect to spend 20 minutes completing online assessments at 3-months, 6-months and 12-months.

Follow-up Health Assessments (30 minutes to 1 hour for 3-month visit, 30 minutes for remaining visits)
Randomized participants will attend an in-person 3-month visit lasting 30-60 minutes, at which they will return the wifi scale and fitbit that the study loaned to them. They will also attend 6- month and 12-month health assessment sessions lasting 30 minutes where we will gather anthropometric data, including weight, height, waist circumference, and BMI, blood pressure, and will administer questionnaires. Participants will receive a handout following the visit detailing their measurements from the visit, for their

future reference. Study staff will remind participants about assessment visits within 1 week prior to the scheduled session. mIf extenuating circumstances prohibit attendance to an in-person session, participants will be mailed equipment to allow for remote assessment to be completed by phone or video conference with an assessor. Participants will also complete the study questionnaires and surveys via REDCap links.

Exit Surveys (10 minutes)
Participants will complete an exit survey during the 3-month and the 12-month assessment sessions to elicit general feedback about the study, as well as any potential confounding variables. The exit surveys will examine intervention component preference and perceived usefulness of intervention features.

Results Session (1½ - 2 hours)
After the conclusion of the trial, all participants will be invited back for an optional one-hour mresults session. Study staff will overview study findings, and discuss study data and conclusions with participants. Results sessions will only include aggregated data from the participant sample. Specific participants' results will not be discussed.

Intervention Components

All participants will have the SMART WFS and online lessons and will be loaned a Fitbit Aria Wi-Fi Smart Scale and Fitbit Zip if they do not already own one. Participants will be randomized to one of two first line treatments: 1) WFS; or 2) WFS+Coaching. If the intervention is maugmented for a participant they could additionally receive coaching, text messages, or meal replacements depending on their initial treatment group and whether they are stepped up mmoderately or vigorously. The intervention components are described below:

Wireless Scale
A loaned wireless scale (i.e., the Fitbit Aria Wi-Fi Smart Scale) will be provided to participants mat an in-person baseline assessment/randomization session where participants will be trained to mself-weigh, daily, for 12 weeks. Training will emphasize weighing upon awakening, after urinating, without clothes. Weight data from the wireless scale will be visible to participants through the SMART App. Participants will return the scale at their 3 month in-person assessment session. Scales will be recalibrated before being assigned to a new participant.

Wireless Accelerometer
A wireless accelerometer (i.e., the Fitbit Zip) will be loaned to participants (if they do not already own one) at an in-person baseline assessment/randomization session. Participants will be instructed to wear the Fitbit Zip, daily, for 12 weeks. Physical activity data from the Fitbit Zip will sync wirelessly to the SMART App, which will display participants' daily physical activity, including steps taken and duration of moderate to vigorous physical activity. To register and use the Fitbit devices, participants will be required to create a Fitbit account and download the corresponding Fitbit App to their smartphone. The SMART App will be linked with participants' Fitbit account to allow physical activity and weight data to be wirelessly transmitted to the SMART app. Syncing will require Bluetooth capability and internet connection. The Fitbit Aria wireless scale and Fitbit Zip were chosen as inexpensive, low- mburden, and easy to use wireless monitoring devices, that are widely accessible to consumers and integrate with the SMART App.

The SMART App
A custom-built native application named The SMART App will be downloaded to participants' smartphones during the baseline assessment/randomization session. The app graphically displays participants' dietary, physical activity, and weight data and goals on the smartphone. Participants will have

an opportunity to self-report dietary intake and physical activity using a search tool built into the app. Activity and weight data collected using the wireless scale and accelerometer will be wirelessly transmitted to the app. The SMART app will not collect or obtain any personal or identifying information from the phone when downloaded. Participants will log-in using a QR code. Participants will be provided with the SMART app during their Tech Training, and can keep the app for the 12-month duration of their time in the SMART study if they give the SMART team permission to continue to collect and analyze the app-generated data.

Training*:* After installing the app, staff will provide instructions on how to use the app to locate and enter foods from the Calorie King nutrient database. Staff will train participants on how to accurately estimate portion sizes. They will also be trained to recognize their moderate to vigorous intensity physical activity and to record it in the app (for times when they do not wear the Fitbit, e.g., swimming, forgetting). Participants will be shown how to enter and change wake time and bedtime for determining time of message delivery. Finally, participants will complete a values card sort exercise that will help determine the content of the text message intervention component. This is described in further detail, below, under Messages; Wake Time messages. They will be asked to enter their daily dietary intake and physical activity into the smartphone, for 12 weeks, and will be permitted to keep the app throughout the full 12-month trial. Time- stamped data from the smartphone will upload automatically to the secure study server, where it will be visible on a dashboard to coaches and study staff in real-time.

Goals*:* All participants will be given the goal of 5% weight loss via calorie reduction from usual intake and increased physical activity. *Dietary Goals* Participants will receive both a calorie goal and a fat goal (based on 25% of total daily calories from fat). Those weighing ≤174 lb. at baseline will be instructed to follow a 1200- kcal/d diet (33g fat); participants weighing 175 to 219 lb. will be advised to follow a 1500-kcal/d diet (42g fat); those 220 to 249 lb. will be asked to follow an 1800-kcal/d diet (50g fat); and ≥250 lb. will be instructed to follow a 2000-kcal/d diet (55g fat). *Physical Activity Goals* Participants will be encouraged to engage in a variety of safe physical activities classified as moderate intensity by the Compendium of Physical Activities. Participants will be instructed to track bouts of 10 minutes or more of moderate to vigorous physical activity on the app. Physical activity will also be objectively measured using a wireless accelerometer (i.e., Fitbit Zip) that will be loaned to participants. Participants will be given a physical activity goal that will be personalized on a week to week basis starting at 60 minutes per week. Increases in target physical activity will be tailored based on progress from the previous past two weeks.

Online Lessons

Participants will be asked to complete 12 online lessons based on the DPP (e.g., self-monitoring, portion size estimation, fat and calorie content of foods, meal and snack patterning, becoming active, social support for physical activity, stimulus control). Participants will log-in using their user id and password. User ids will not contain any personal or identifying information. Participant engagement data with the online lessons will be collected. This information will be used to complete the cost effectiveness analysis (exploratory aim). Our secure study server will house programmed algorithms that (a) receive participant data from The SMART App and transform it to an interpretable, user-friendly format that coaches view in real time; (b) guide the delivery of intervention components to subjects; (c) identify treatment nonresponse, alerting the participant, study team, and/or coach of the new actions they need to take; and (d) guide the delivery of behavior responsive text messaging to participants, as described below.

Telephone Coaching (WFS+C)

In addition to receiving the SMART WFS, participants randomized to a coaching condition will receive weekly telephone coaching sessions from a health promotionist (study lifestyle coach).

Telephone coaching sessions will last approximately 10-15 minutes and include motivational interviewing, feedback on self-monitoring and goal attainment (observed from uploaded diet and activity data), and problem solving about barriers. The coach will review calorie, fat and physical activity goal attainment, discuss barriers, problem-solve, and support the participant in refining goals and action plans. Frequently discussed dietary strategies include portion control, use of lower-calorie substitutes, increased intake (within calorie allowance) of fruits and vegetables, or (per randomization) use of meal replacement products. Physical activity strategies involve recommending enjoyable activities that can be fit into a daily routine, categorizing intensity by MET value.

Messages

Participants randomized to receive messaging will receive up to 3 tailored push notification messages per day. Within the messaging intervention component, message content will be randomized at three time points daily (wake time, midday, evening), delivered 6 hours apart.

Wake time messages: Messages delivered at participants' wake time will randomly focus on weight or physical activity self-monitoring. Message delivery will be randomized based on one of the following three strategies: 1) no text message, 2) generic text message, 3) values- based text message. Values-based messages will be derived from Maslow's hierarchy of needs (i.e., physical well-being, social/ affiliation, and self-actualization). During tech set-up and training, participants will complete a card sort exercise where they will be presented with a card representing each value. Participants will then be asked to sort the values in order of personal importance, from most important to least important. Participants will receive values-based messages based on their chosen personal value that has the greatest bearing on their lifestyle.

Midday messages: Midday messages will be delivered 6 hours following participants' reported wake time. Message content will focus on dietary intake self-monitoring. As described above, message delivery will be randomized as follows: 1) no message; 2) generic message; 3) values-based message.

Evening messages: Evening messages will be delivered 1 hour before the time that participants report as their usual bedtime. Message content will focus on next day calorie goal attainment. Message delivery will be randomized as follows: 1) no message; 2) unstructured calorie goal attainment strategy. Participants who receive an "unstructured" message will be prompted to enter a strategy for attaining next day's calorie goal in a free text field within the SMART app. Participants receiving a "structured" message will be prompted to select a strategy for attaining next day's calorie goal from a list of options presented in the message.

Meal Replacement

Participants randomized to receive meal replacements will be provided with commercial meal replacement products for the remainder of the 12-week intervention period. Information will be provided to participants on incorporating meal replacements to replace meals. Participants will receive meal replacements equivalent to 2 meals per day in the form of powder to make meal replacement shakes.

Study Retention Plan

To prevent attrition, study staff will develop good rapport with participants during recruitment and maintain the relationship throughout the study, including sending birthday cards, holiday cards, newsletter, and appointment reminder postcards.[26] In order to maintain participant confidentiality, all study related-materials that are sent in the mail will be in a sealed envelope, without any study-specific information or identifiers on the envelope. Participants are provided with a phone number to call immediately if they encounter any tech issues with the application. Staff will convey reminders of scheduled assessments by email or by phone. Participants also will be incentivized $20 to complete their 3-month assessment, $40 to complete their 6-month assessment, and $60 to complete their 12 month assessment, for a potential total of $120.They will be provided with a free parking voucher for any in-person sessions. Participants also will identify two locator people that may be notified if contact with the study participant is lost. Locator people will be associates of the participant who do not live in the same household as the participant and who agree to serve as emergency contacts for the participant. Participants will be asked to obtain permission from their associate to serve as a locator person. We will ask participants to provide their locator people with a link to our REDCap Locator Person Survey, where the locator person may agree or decline to serve as an emergency contact. Only those who agree to serve as an emergency contact will provide their contact information. We will only attempt to contact a locator person if we are unable to reach an active participant after 3 phone call attempts and a final email attempt, or in the event of an emergency. After these initial attempts to contact the participant, we will attempt to contact the participant's designated locator people. We will make two phone call attempts to reach a locator person. If we are unable to reach the locator person, we will attempt to leave a voice mail. If the locator person also provided an email address, we will send a final follow-up email. If unable to reach participant after these methods, we will send a letter to the participant. Participants who are not randomized to coaching calls and do not record anything in the WFS for one week will be called by a staff RA. After the first 8 weeks of the intervention, the participant will be called if there are 2 weeks of no WFS activity. These methods have proven effective in promoting participant retention in our prior studies. Based on these prior studies, we expect the attrition rate in the current study to be approximately 10% by month 6.

Assessment Only Participation

In the event a participant expresses interest in discontinuing the intervention portion of the study, only, we will offer the participant the option of assessment-only participation. Assessment-only participation is low burden and provides participants with the option to stay engaged in the research process. Participants who decide to continue assessment-only participation will complete their online assessments and in-person assessmcomplete assessment sessions as originally scheduled. Participants will receive the appropriate compensation for completing each assessment session (described in Section 12.0). Assessment-only participants will only be contacted for scheduling/retention, and will not receive further communication about the intervention components.

Study Timeline

An individual participant is anticipated to be enrolled in the SMART study for the duration of 12 months. Participants will be asked to complete in-person baseline, 3 month, 6 month, and 12 month health assessment sessions. Participants will be asked to complete intervention components, remotely, for 12 weeks.

Study Measures Screening Tools

questionnaires ask about demographics, anthropometrics, motivational readiness to change, physical activity readiness, and scheduling availability. The Physical Activity Readiness Questionnaire (PAR-Q),[27] designed for adults aged 15-69, asks about 7 activity risk factors (e.g., chest pain, dizziness, joint problems). The Primary Care Evaluation of Mental Disorders (PRIME-MD), Patient Health Questionnaire (PHQ),[28] and MINI Alcohol and Substance Abuse/Dependence module will be administered to screen out candidates whose suicidality or bulimia could place them at risk in a weight loss trial, or whose uncontrolled substance abuse or binge eating disorder could interfere with program adherence. Changes to health status, medications, and enrollment in a formal weight loss program will be ascertained at health assessment sessions (baseline, 3, 6, and 12-month) to ensure participants maintain compliance with eligibility.

Primary Outcome

Weight will be measured in the lab at baseline, 3, 6, and 12 months months. The primary outcome is weight loss at 6 months. Weight will also be measured at month 12 to examine how well the benefits achieved by months 3 and 6 are maintained (tertiary Aim 3). Measurements will be taken without shoes, wearing light clothing on a calibrated beam balance scale. Participants will self-weigh, daily, for the duration of the 12 week intervention period, using the Aria wireless scale. Participants will receive push notification reminders to self-weigh.

Additional Physiologic Outcomes

Height will also be measured using a stadiometer, and BMI will be calculated. Waist circumference, a correlate of abdominal visceral fat also will be assessed. Measurement will be done twice during expiration, taking the average for analyses, by positioning an anthropometric tape midway between the palpated iliac crest and the palpated lowest rib margin in the mid-axillary lines. Blood pressure will be measured three times, with each reading taken 30 seconds apart. The average of the second and third readings will be obtained for analyses.

Exploratory Moderators

Age will be obtained from a demographic questionnaire.[29] SES will be measured using a subset of questions from The Behavioral Risk Factor Surveillance System, a valid and reliable national survey of risk behaviors and preventive health practices. Items will measure participants' marital status, employment status, annual income level, household size, and MacArthur Scale of Subjective Social Status. Self-Efficacy will be assessed from the scenario- based Dieting Self-Efficacy Scale.[30] The DIET-SE includes 11 items, broken down into three subscales to reflect different kinds of challenges to eating self-control: 1) high caloric food (HCF, 4 items), 2) social and internal factors (SIF, 4 items), and 3) negative emotional events (NEE, 3 items). The internal consistency of the DIET-SE is satisfactory (α = .77 for HCF; α = .79, 4 items; and α = .79 for NEE; total score α = .87). Test–retest correlations for a 2- to 3-week interval were r = .83 for the DIET-SE scale (r = .75 for the HCF, r = .77 for the SIF, and r = .80 for the NEE subscale), indicating good test–retest reliability. The Self-Efficacy of Exercise Behavior Change[31] measure includes 18 items. Participants use a 5-point Likert scale (1 = not at all confident; 5 = completely confident) to rate how confident they are that they will be able to exercise when "other things get in the way" such as being depressed, anxious, busy, or tired

Standardized screening

Exploratory Mediator

Autonomous Motivation will be measured by an adapted and abbreviated version of the Treatment Self-Regulation Questionnaire.[32,33] Four statements will be rated on a 5-point scale ranging from 1 (not at all true) to 5 (very true). Each item begins with the same stem: "The reason I want to achieve a healthier weight is…", followed by, for example, "…because I personally believe it is the best thing for my health." The abbreviated scale shows satisfactory internal consistency (α =.77).[33]

Cost Effectiveness

We will create a detailed accounting system to capture all costs associated with implementation of treatments.[34] Using a societal perspective, we will include patient costs associated with time spent engaged in treatment (e.g., while receiving telephone coaching, using WFS, engaging with weekly lessons) and transportation costs associated with in-person visits. Salary and fringe benefit information obtained from the U.S. Department of Labor, Bureau of Labor Statistics will be used to calculate total expenses associated with personnel. We will also measure health-related quality of life at baseline, 3 months, 6 months, and 12 months via the 5-item EQ-5D[35] and SF-12 Health Survey, whose scores we convert to quality-adjusted life years (QALYs).[36] We will measure absenteeism and presenteeism at baseline, 3 months, 6 months, and 12 months using the WHO HPQ-Short.

Table 1: Assessment Measures Schedule

	Measure	Screening/ Baseline	12 week intervention	3 months	6 months	12 months
Primary Outcome	Weight	x	x	x	x	x
Additional Physiologic Outcomes	Height, BMI, waist circumference, blood pressure	x		x	x	x
	Participant at home weight		x			
Exploratory Moderators	Demographics	x				
	SES The MacArthur Scale of	x				
	Subjective Social Status					
	Self efficacy	x		x	x	x
Exploratory Mediator	Autonomous Motivation	x		x	x	x
Cost-Effectiveness	Costs associated with intervention (Participant time spent engaged in treatment; Personnel)		x			
	Health-related quality of life (EQ-5D and SF-12)	x		x	x	x
	Absenteeism/Presenteeism (WHO-HPQ-Short)	x		x	x	x
Screening Tools	Physical Activity Readiness (PAR)	x				
	Readiness to Adopt Weight Control Behaviors Scale	x				
	Primary Care Evaluation of Mental Disorders (PRIME-MD)	x				
	Patient Health Questionnaire (PHQ)	x				
	MINI Alcohol and Substance Abuse/Dependence module (MINI)	x				

Establishing and Maintaining Treatment Fidelity

Manual of Operations

A MOP has been prepared to guide implementation of all aspects of the protocol including: a) screening, b) pre-randomization equipoise induction to equalize the desirability of all treatment conditions; c) initial WFS and equipment training; d) assessment protocols; e) coaching sessions; and f) augmentation randomization.

Coaching Fidelity

Telephone coaching sessions will be audiotaped and a 15% sample rated for treatment fidelity on a quarterly basis. If fidelity falls below 90%, coaches will be retrained. Fidelity checklists specify: a) good counseling practice (e.g., positive regard, active listening); b) intended session content (e.g., addressing goal attainment of activity and diet; SMART goal setting); and c) unintended session content (i.e., contamination such as evidence of recommending meal replacement to a participant not assigned to WFS+C+T+ MR). Dr. Pfammatter will train the coaches on the intervention and will serve as a primary fidelity evaluator. Training will initially involve role- play as coach and participant. Next coaches will observe the Co-I and Coordinator performing sessions with volunteers. Finally each coach will perform a live dress rehearsal of telephone delivery of each treatment session and condition. They will continue to rehearse until fidelity ratings show that each coach can be certified as competent to deliver all sessions for all conditions. Recordings of the trainings will be made and retained in case there is a need to train new coaches or retrain existing ones. Coaches will meet weekly as a group with Dr. Pfammatter and/or Dr. Spring for clinical supervision.

Augmentation Randomization Fidelity

Research staff will check weekly to ensure that participants who are eligible are re-randomized.

App Use Fidelity

If a participant does not appear to be using the app staff will follow the MIA protocol to ensure that the app is functioning properly.

Data Analysis

Intent-to-Treat

All subjects, once randomized, will be included in the intent-to-treat sample. Every effort will be made to collect all primary and secondary outcomes even if a participant does not engage in assigned treatments.

Statistical Analysis

Analyses will be conducted on an intent-to-treat basis, using all available data from all randomized participants. To determine whether initial WFS alone is noninferior to initial WFS+C, we will compare these two initial treatments (regardless of subsequent treatments) on the primary outcome: weight change from baseline to 6 months, and on two exploratory outcomes (weight change from baseline to 3 and 12 months), controlling for sex, and using 90% CIs. All other analyses will be conducted as superiority comparisons and use 95% CIs. To determine whether a Vigorous Step-Up is superior to a Modest Step-Up, we will compare the effects of the two augmentation tactics on weight loss, controlling for sex and weight change since baseline, and test whether their impact varies by initial treatment. We will use a Covariance Pattern Model (CPM[37]) via SPSS MIXED to analyze the longitudinal weight data. CPM allows for incomplete data across time and, under maximum likelihood estimation, accommodates data missing at random.[38] CPM includes fixed effects for time indicators (with baseline as the reference) and the group by time indicator interactions. An unstructured residual variance-covariance matrix allows differing variances and covariances across time. We will also use the weight and replicate method[22] to find the optimal sequence of treatment tactics by comparing the effect on weight loss from baseline to month 6 of the four treatment sequences embedded in the SMART trial.

We will use CPM for pre-specified exploratory analyses examining whether initial treatment effects differ by demographic characteristics and whether end-of-treatment differences in weight loss maintain through 12-month follow-up.

Separate mediation analyses will examine whether self-monitoring adherence and changes in self-efficacy and autonomous motivation from baseline to 3-months mediate the initial treatment effect on weight loss during the same period. Using a counterfactual framework[39], the total effect of treatment on 3-month weight loss will be decomposed into natural direct and indirect effects. We will report the percent mediated: the ratio of the natural indirect effect divided by the total effect. CIs for the percent mediated will be obtained using a bias-corrected bootstrap[40] with 5000 bootstrap samples.

Primary Aim Analysis

The primary aim is to test whether a mHealth intervention (i.e., WFS alone) is an adequate first line treatment for obesity, versus whether more resource-intensive intervention that includes human support (WFS+C) is needed from the outset of treatment to engage participants and maximize weight loss across the treated population. We hypothesize that starting with WFS alone will be noninferior to WFS+C for the primary outcome of 6-month weight loss. The Analysis of the Primary Aim will compare initial WFS (regardless of the subsequent augmentation tactics) to initial WFS+C on change (decrease) in weight (primary outcome) from baseline to month 6. There are a total of 3 measurement occasions for this analysis: weight loss measured at baseline (time=0), 3 months (time=3), and 6 months (time=6). As indicated above, CPM using SPSS MIXED will be used to analyze the longitudinal data. CPMs use all available outcome data, allowing subjects to have an unequal number of observations, and accommodating missingness when the response is missing at random. The analysis will fit a CPM with fixed effects for the intercept, time indicators (with baseline as the reference), group-by-time indicator interactions. The group indicator will be defined as WFS (cells A+B+C in Figure 1) vs. WFS+C

(Cells D+E+F in Figure 1). The interaction of group by the 6 month time indicator will be used to assess this aim.

Secondary Aim Analysis

The secondary aim was to test whether suboptimal responders to first-line treatment are rescued more effectively (achieve greater weight loss) when given vigorous (resource-intensive) treatment augmentation with both a traditional weight loss component they have not yet received (coaching or meal replacement [MR]) and mHealth messaging, as compared to modest (minimally resource- intensive) augmentation with messaging alone.

The analysis of the Secondary Aim will compare the two subsequent augmentation tactics for non-responders, namely Modestly Step-Up vs. Vigorously Step-Up on change (decrease) in weight from baseline to month 6. This analysis will be similar to the Aim 1 analysis, but (a) will include only non-responders to the first-line treatment; and (b) the group indicator will be defined as Modestly Step-Up (cells B+E in Figure 1) vs. Vigorously Step-Up (cells A+D in Figure 1).

Tertiary (exploratory) Aim 1 Analysis

An exploratory aim examined baseline demographics as moderators, and self-efficacy, autonomous motivation, and self-monitoring adherence as mediators of treatment response.

Moderators. To identify baseline demographic variables (sex, age, SES, race and ethnicity) that moderate treatment effects and to examine whether between-treatment differences in 6-month weight loss are mediated by extent of self-monitoring and by changes in self-efficacy and autonomous motivation. . The analysis for this aim includes two parts. The first part is designed to construct an individualized, stepped-care sequence by identifying moderating variables at baseline (e.g., SES, baseline self-efficacy, baseline emotional eating) that predict who will benefit more or less from WFS vs. WFS+C. The second part I designed to identify time-varying moderators (e.g., self-monitoring during the initial treatment period, changes in self-efficacy) that could be used to further individualize the augmentation tactics. To do this, we will apply Q-learning[23,41] which is a generalization of moderated regression analysis to sequences of treatments. The overarching goal of this analysis is to (empirically) generate a candidate sequence of treatments that is more deeply tailored than the 4 treatment sequences embedded in the SMART (i.e., the 4 treatment sequences listed in Table 1). By "more deeply tailored", we mean a sequence of treatments in which the optimal first-line treatment (i.e., WFS vs. WFS+C) depends on baseline variables and/or other patient characteristics (e.g., gender, age, SES); and/or the best augmentation tactic for non- responders (i.e., Modest vs. Vigorous Step-Up) depends on what type of non- responder the individual is (e.g., a non-responder who does not self-monitor vs. a non-responder who does self- monitor). Q-learning will be used to identify moderators and to develop an optimal stepped-care sequence of treatments that maximizes weight loss over a 6 month follow-up.

Mediators. The second part is designed to ***examine the role of increased autonomous motivation, increased diet and physical activity self-efficacy, and self-monitoring adherence as mechanisms (mediators*)** by which first-line treatment (WFS vs. WFS+C) has an impact on weight loss. Two conditions must be met for establishing such mediation: 1) an effect of first- line treatment on longitudinal autonomous motivation, self-efficacy, and self-monitoring; and 2) longitudinal autonomous motivation, self-efficacy, and self-monitoring, in turn, have effects on longitudinal weight.[42] The first effect will be tested By regressing the mediator on the first-line treatment indicator variable. These analyses will compare initial WFS (regardless of the subsequent augmentation tactics) to initial WFS+C

on change (increase) in autonomous motivation and self-efficacy (longitudinal mediators) from baseline to month 3 (the time when coaching ended and scales and fitbits were returned). These mediators are calculated as the difference at 2 measurement occasions: autonomous motivation and self-efficacy measured at baseline (time=0) and 3 months (time=3). Self-monitoring of diet, physical activity, and weight was not measured at baseline, but was measured daily between baseline and month 3. Daily self-monitoring data were aggregated across the 3 month treatment phase to evaluate whether self- monitoring differs across initial treatments and is associated with 3-month weight loss.

Mediation will be assessed using counterfactual framework[39] in which the total effect of treatment on 3-month weight loss will be decomposed into natural direct and indirect effects. To calculate the natural indirect effect, we will estimate two models. The first, as described above, is a regression of the mediator on first-line treatment. The second model is a regression of weight loss at 3-months on both the mediator and treatment indicator. The indirect effect is calculated as the product of the coefficient on treatment in model 1 times the coefficient of the mediator in model 2. The direct effect is the coefficient of treatment in model 2. We will report the percent mediated: the ratio of the natural indirect effect divided by the total effect where the total effect is the difference in 3-month weight loss between first-line treatment conditions, estimated by regressing weight change on treatment condition. CIs for the percent mediated will be obtained using a bias-corrected bootstrap[40] with 5000 bootstrap samples.

Tertiary (exploratory) Aim 2 Analysis

A second exploratory aim examined whether treatment differences in weight loss at the end of the 3-month intervention period were maintained through final follow-up (12 months).

To investigate ***how well the health behavior changes produced by the different treatments maintain through 12 months*** of follow-up. The Analysis of this Aim will compare initial WFS (regardless of the subsequent augmentation tactics) to initial WFS+C on change (decrease) in weight (primary outcome) from baseline to month 12. There are a total of 4 measurement occasions for this analysis: weight loss measured at baseline (time=0), 3 months (time=3), 6 months (time=6), and 12 months (time=12). CPM using SPSS MIXED will be used to analyze the longitudinal data. CPMs use all available outcome data, allowing subjects to have an unequal number of observations, and accommodating missingness when the response is missing at random. The analysis will fit a CPM with fixed effects for the intercept, time indicators (with baseline as the reference), group-by-time indicator interactions. The group indicator will be defined as WFS (cells A+B+C in Figure 1) vs. WFS+C (Cells D+E+F in Figure 1). The interaction of group by the 12 month time indicator will be used to assess this aim. WFS

Tertiary (exploratory) Aim 3 Analysis

Best treatment sequence. To find the optimal sequence of treatment tactics by comparing effects on 6 month weight loss and cost-effectiveness (cost/pound lost) of the four treatment sequences embedded in the SMART design. The analysis for this exploratory aim includes two mparts. The first part focuses on comparing treatment sequences in terms of weight loss. This analysis will compare the 4 treatment sequences embedded in the SMART study on change (decrease) in mweight from baseline to month 6. Table 2 describes these 4 treatment sequences (TS's) and the mexperimental conditions (cells). The Weight and Replicate method (W&R)[22,43,44] will be used to

compare the 4 TS's. W&R employs standard regression analysis, with a small adjustment involving weighting and replication. Weights are needed given that by design (i.e., since non-responders are randomized twice whereas responders are randomized only once), non- responders are under- represented in the observed data corresponding to each of the embedded TS. To account for this under-representation, weights that are inversely proportional to the probability of being offered a particular sequence of treatments will be assigned. Replication is necessary, given that each

Table 2. The four treatment sequences (TS's) embedded in the SMART study in Figure 1

Embedded Treatment sequences (TS)	Initial treatment	Subsequent tactic (treatment) for non-responders	Subsequent tactic for responders	Subgroups in Figure 1
1	WFS	Modestly Step-Up (WFS+T)	Continue first-line intervention	B+C
2	WFS	Vigorously Step-Up (WFS+T+C)		A+C
3	WFS+C	Modestly Step-Up (WFS+C+T)		E+F
4	WFS+C	Vigorously Step-Up (WFS+C+T+MR)		D+F

responder is consistent with two TS's: Responders to WFS (subgroup C) are consistent with TS #1 and TS#2; and responders to WFS+C (subgroup D) are consistent with TS #3 and TS #4. To account for this design feature, prior to data analysis the outcomes (and covariates) for all responders will be replicated twice. Replication improves the statistical efficiency (power) in the comparison of embedded TS's by allowing the correlation between baseline covariates and the outcome to be pooled across TSs. Robust standard errors are used to account for the "double use" of the responders.[45]

The second part will focus on ***comparing treatment sequences in terms of cost-effectiveness.*** A cost-effectiveness analysis for comparing the four treatment sequences will be conducted from a societal perspective. Intervention costs include personnel (e.g., lifestyle coach time) and materials (e.g., meal replacement product) costs associated with developing and delivering all four sequences. The principal measure of cost-effectiveness will be incremental cost per pound lost. This ratio will be calculated by taking the difference in average costs per patient involved in any two of the treatment sequences divided by the difference in weight loss between the two groups. A second effectiveness measure we will use is health- related quality of life, measured via the 5-item EQ-5D[35] and converted to quality-adjusted life years (QALYs)[36]. We will derive the incremental cost per QALY between each pair of treatment sequences.

An advantage of deriving cost per QALY is that it will enable us to compare the incremental cost- effectiveness of the treatment sequences to other behavioral treatments.[46] No discount rate will be applied because the interventions occur within the same one-year time period. Bootstrapping will be used to estimate the uncertainty of each incremental cost-effectiveness ratio.[47]

Missing Data

Every effort will be made to obtain complete data from all participants; however some missing data are likely. CPM does allow missing data and provides valid results under the assumption of missing at random (MAR). MAR means that the missingness can be related to

model covariates as well as observed values of the dependent variable, and is sometimes termed "ignorable" missingness. As Molenberghs et. al.[48] detail, MAR is a relatively weak and non-restrictive assumption. Nonetheless, the possibility of non-ignorable missingness cannot be ruled

out and so, as advocated by Molenberghs et. al.[48] we will conduct sensitivity analyses using non-ignorable pattern- mixture and selection models to investigate the robustness of our conclusions across these different models for missing data. This approach will follow the detailed exposition in Hedeker and Gibbons.[49]

Sample Size and Power

Sample size calculations for this study are based on the Primary Aim contrast: baseline to 6-month weight change for initial WFS versus WFS+C. The hypothesis is that 6-month weight loss with WFS alone as initial treatment is noninferior to WFS+C. Following guidance[50] for a non-inferiority margin to be 50% of the difference between a treatment and control condition, non-inferiority will be considered established if the lower limit of a $(1–2\alpha) \times 100\%$ confidence interval (CI) for the mean difference in weight loss between WFS alone and WFS+C is above $–\delta$, where α is the Type I error, and δ is the non-inferiority margin. Per recent evidence of a 5.1 kg difference between similar treatment groups at 6 months[51], we define the non-inferiority margin as 50% of that difference: 2.5 kg. That margin aligns with conclusions of a Cochrane Systematic Review and meta-analysis that the 6-month weight loss difference between face-to-face vs. interactive computer-based obesity interventions should exceed 2.1 kg to be clinically important.[52]

Based on preliminary data, we assume an overall SD of 13.5 with 0.80 within-person correlation between baseline and month 6 weights. To obtain 90% statistical power to establish noninferiority of WFS versus WFS+C with 1-sided alpha equal to 0.05, we estimate needing 344 participants. Assuming month 6 attrition up to 14%[53], recruiting 400 participants, yielding 172 participants in each initial arm after attrition is estimated to provide adequate power for the primary contrast.

Although sample size determination for this trial is based on the primary aim as described above, ***we will also have adequate power to test the secondary aim***. The primary contrast in the secondary aim data analysis tests the hypothesis that Vigorous augmentation of treatment tactics for non-responders will be superior to Modest augmentation in its effect on change (decrease) in weight from baseline to month 6. Assuming 50% non-response rate, we estimate that 86 participants will be randomized to each of the two augmentation arms. Based on a Type-I error rate of 0.05 (two sided), we will have 82% power to detect a small to medium difference (Cohen's d=0.30) between the two augmentation tactics for non-responders.

Data Collection Schedule

The study timeline and recruitment goals appear in Table 4. Quarters 1-4 will be dedicated to completing development of the protocol and study tools. Development activities include completing the programming necessary to transmit weight data wirelessly to a smartphone application, preparing treatment manuals and fidelity check protocols, and training coaching staff. Recruitment, screening, and randomization activities will commence in Year 2, Quarter 1 and continue through Year 4, Quarter 3. Enrolled participants will complete the protocol and follow-ups until Year 5, Quarter 3 and the remainder of Year 5 is for data analyses and report writing.

Table 4. Study Timeline and Participant Recruitment

	Quarter 1	Quarter 2	Quarter 3	Quarter 4	Total
Year 1	Intervention Development				(0)
Year 2	Recruit	40	40	40	(120)
Year 3	40	40	40	40	(160
Year 4	40	40	40	Enrolled	(120)
Year 5	Finishing	Protocol	Data cleaning & analysis		(0)
					N=400

9.0 Incomplete Disclosure or Deception:

Full disclosure will be made of the nature and potential risks of participating in SMART and the study supplement.

10.0 Recruitment Methods:

Recruitment Strategies

Recruitment will target the channels that have proved successful in our prior studies. These include posting: a) flyers at downtown area worksites, clinics, and schools; b) relevant websites related to weight loss, health, nutrition, and physical activity that we will solicit to "post" current approved flyers and ads on their sites; c) health registries (Illinois Women's Health Registry at Northwestern University, NU NUCATS, ResearchMatch); d) relevant local health fairs with information booths/tables where flyers will be available with staff to answer questions; e) use of the Enterprise Data Warehouse (EDW), a joint initiative of NMFF, NU, and NMH, to recruit patients directly from Northwestern Memorial Hospital's General Internal Medicine Clinic; f) Chicago Transit Authority bus and subway advertisements; g) contact former study participants who agreed to be re-contacted for future studies; h) once enrollment for our existing study, Opt-In, has completed, individuals who have expressed interest in participating in our weight loss trials will be given information about the SMART study; i) clinicaltrials.gov and NU Preventive Medicine website will list study eligibility criteria and requirements, and will provide the study website link and contact information. The project's website provides a link to a REDCap document where interested candidates may consent to be considered for research participation, complete an on-line screening questionnaire and provide good contact times. Eligible candidates will be contacted to arrange for a telephone pre-screening interview.

Recruitment Tracking

Research staff will track all participants recruited for the study. Participants will initially complete a web survey using REDCap. Data from REDCap will be downloaded, and descriptive statistics will be generated. Information to be collected will include participant name, screening date, date of birth, race, ethnicity, self-reported height, self-reported weight (BMI will be automatically calculated), screening status, and reason for exclusion.
A bi-weekly progress meeting will take place to review recruitment, retention, and strategies for ensuring the project remains on target with respect to accruals and retention. The project coordinators, and Investigators, Dr. Spring, Dr. Pfammatter and Dr. Nahum-Shani will attend these meetings.

Inclusion of Women and Minorities

Women will constitute at least 50% of the sample. Pilot data from a previous weight loss trial support the expectation that the sample will be approximately 60% White, 32% African American, 8% other minority. Approximately 20% will be Hispanic or Latinx. Targeted

recruitment of minorities has not been necessary to attain substantial, representative minority enrollment because the Chicago area population is so diverse.

11.0 Consent Process:

Potential participants will attend an equipoise Orientation session where they will learn details about the study. The Orientation will take place at Northwestern University on the Chicago campus. All candidates will have an opportunity to approach study staff with questions prior to providing consent. Candidates may also confer with their own physician and/or family members prior to providing consent. Candidates will read and sign the consent form for the study on a REDCap form and may do this at any time after the Orientation.

Informed consent will be obtained before entry into the study from any participants who may be randomized if eligible. Full disclosure will be made of the nature, and potential risks and benefits related to participation in the SMART trial. All consent forms have been developed according to the requirements of the Northwestern Institutional Review Board (IRB). The consents must be signed and submitted prior to the Pre-Randomization Phone Call. Candidates will sign the consent documents housed in REDCap. A PDF version of the consents will be uploaded to Study Tracker and given to the participant. The informed consent documents will include the following components:

1. A statement that the study involves research, an explanation of the purpose of the research, the expected duration of the individual's participation, a description of the procedures, and identification of any experimental procedures.
2. A description of any reasonably foreseeable risks or discomforts to the participants.
3. A description of any benefits to the participants (or to others) that may reasonably be expected from the research.
4. A statement describing the extent to which confidentiality of records identifying the participant is maintained.
5. An explanation as to whether any compensation or medical intervention is available if injury occurs and, if so, what it consists of, or where further information may be obtained.
6. An explanation of whom to contact for answers to pertinent questions about the research and the participant's rights, and whom to contact in the event of a research-related injury to the participant.
7. A statement that participation is voluntary.
8. A statement that allows for the participant to agree or disagree to be audio recorded during telephone coaching sessions.
9. A statement that allows for the participant to agree or disagree to be contacted for future follow-ups to the study or other future studies within our research group.

Non-English Speakers: will be excluded from the study as they will not be able to interact with the health behavior coaches over the telephone.

Participants who are not yet adults (infants, children, and teenagers): we will not be enrolling persons who are under the age of 18.

Cognitively Impaired Adults: this population will not be included in this study.

Adults Unable to Consent: this population will not be included in this study.

Consent Addendum

Changes regarding the length of the 3-month follow-up assessment were made after some participants had consented to participate in the study, but had yet to complete their 3-month visits (at the onset of the study the 3-month assessment visit was anticipated to take 30 minutes to complete; as the study continued, we learned that the visit takes 30 minutes to an hour to complete). As a result, a consent addendum will be completed with select participants to describe the new information and provide them with the opportunity to consent to the study changes. The addendum will include the following components:

1. A description of the change in study procedures, to reflect that the 3-month visit takes 30 minutes to an hour to complete rather than only 30 minutes.
2. A statement that participation is voluntary.
3. An explanation of whom to contact for answers pertinent questions about the research and the participant's rights, and whom to contact in the event of a research-related injury to the participant.
4. A statement that there are no changes to the foreseeable risks or discomforts to the participants.
5. A statement describing the extent to which confidentiality of records identifying the participant is maintained.

Any participants who enrolled in the SMART study but did not complete their 3-month visit before the noted changes were implemented will be provided with the consent addendum in a phone call. The phone call will take place prior to their 3-month assessment visit. These participants will have the opportunity to ask questions of the study staff prior to providing consent. They may also confer with their own physician and/or family members prior to providing consent. Participants will provide verbal consent to the study staff during the phone call, which will be documented on a RedCap form.

12.0 Financial Compensation:

Participants will receive compensation for their time. Compensation includes $20 for completing the 3 month assessment, $40 for completing the 6 month assessment, and $60 for completing the 12 month assessment, for a possible total of $120. The payments will be issued at each assessment visit in cash. If the participant completes an assessment remotely instead of in-person, they will be compensated with a stored value card. Additionally, participants who plan to drive to in-person sessions will receive a free parking voucher on the day of the scheduled session.

There will be no provisions for compensation of the purchase of smartphones or mobile phone plans.

13.0 Audio/Video Recording

Audio Recordings: Coaching Fidelity

All telephone coaching sessions will be audio recorded in order to conduct treatment fidelity checks. If participants have not consented to have their calls audio recorded, study staff will ensure that their recorder is unplugged from the telephone jack such that only their own voices will be recorded. A 15% sample of the calls will be rated for treatment fidelity on a quarterly basis. Recordings of the trainings will be retained in case there is a need to train new coaches or retrain existing ones.

All audio recordings will be coded with anonymous study IDs and saved on the password-protected, secure server. Access will be restricted to authorized personnel and study staff. At the end of the study, all audiotape recordings will be destroyed.

14.0 Potential Benefits to Participants:

Participants are not likely to have any direct benefit from being in this research study. However, they may experience positive changes to their health and mood based on the lifestyle changes they make.

15.0 Risks to Participants:

Participant Risks

Overall, the risks of participation in this study are small. Participation in this study may include the following risks:

1. Participants may experience discomfort due to the types of questions asked during the assessments and interviews, and some may find the questionnaires frustrating and time-consuming. The participants will not be required to answer questions or discuss topics that make them feel uncomfortable.
2. There is a small risk that subjects might experience physical discomfort, such as muscle soreness, pain, or injury, from engaging in or increasing moderate intensity physical activities. Participants will be encouraged to stretch, and exercise in a safe and reasonable manner.
3. There is a risk participants may experience feelings of hunger and deprivation from decreasing calorie and fat intake.
4. There is a potential risk of food allergies from meal replacements. Participants will be asked to report any pre-existing food allergies prior to being provided meal replacements. The study team will obtain meal replacement options to meet participants' dietary needs, therefore participants will not be excluded from the study solely due to the presence of a food allergy/intolerance. Participants who experience food allergies as a result of using meal replacements during this study will be asked to discontinue use of the product, and to notify their physician and study team immediately.

Protections Against Risk

To reduce risk, project staff will be supervised by licensed clinical psychologists (Drs. Bonnie Spring and Angela Pfammatter), and the team includes an exercise physiologist (Drs. Christine Pellegrini). Candidates who are judged, based on screening measures, to have medical or psychological conditions that might make participation injurious will not be enrolled. Participants are further encouraged to contact the PI at any time should they experience significant distress. The measures to be used have been tested in a variety of research programs without problems reported due to their use. However, the participant may terminate the procedureat any time and referrals may be made to the local psychological and medical services as needed. To participate in this study, participants must provide written informed consent using procedures reviewed and approved by the IRB. This consent covers screening visits, intervention, and assessments.

Participants' blood pressure will be taken at baseline and during each assessment visit. In the

event of a high blood pressure reading a study staff member may contact the participant's physician or an on call study physician in order to determine the best course of action. Participants refusing treatment following an elevated blood pressure will be asked to complete an elevated blood pressure waiver. Any participant that refuses treatment following an elevated blood pressure (>180/120) during the study, or a medical adverse event, which makes it no longer medically safe for the individual to participate in the SMART study, will be withdrawn from the study.

Withdrawal

Participants may withdraw from the study at any time. Permission will be sought to continue to collect outcome data for use in the analysis. However, all participants randomized to the intervention will be accounted for in all follow-up analyses following the intent-to-treat principle. If participants withdraw from the study and do not agree to return for follow-up assessments, their assessment data will be multiply imputed from their prior data.

Some participants may be interested in discontinuing the study intervention, but are willing to complete study assessment visits. If this occurs, we will offer the option for these participants to stay engaged in the research process by completing assessments without having to complete other study activities. We will only continue to contact these individuals for scheduling or reminders about assessment appointments. Although participants who choose to only complete assessments will continue to receive the appropriate compensation, the amount of compensation provided is nominal and not does not place undue coercion on participants to remain in the study.

16.0 Provisions to Protect the Privacy and Confidentiality of Participants and the Research Data:

First, each participant is assigned an anonymous study ID which is then used on all study forms. Only where absolutely necessary to assure data integrity is a participant's name also included on study forms. Second, all study forms and paper records that contain participant information (e.g., address lists, phone lists) are kept in secured, locked areas when not in use. In addition, such materials, when in use, are kept away from public scrutiny. Third, access to all participant data and information is restricted to authorized personnel.

The study staff who will be directly involved in contacting, consenting, and protecting the safety of the individuals involved in this research will have access to the locked cabinets and electronic records that contain participant contact information. Study personnel who will work with data collection and integrity will not have access to the participant's contact information. Access will be restricted by the roles of the personnel registered with the IRB.

Data Management

1. Anthropometric and patient reported outcome data will be collected using an online system (NITRO Study Tracker and REDCap) housed at and maintained by Northwestern University Biomedical Informatics Center (NUBIC) of the Northwestern University Clinical and Translational Sciences (NUCATS) program. Paper versions of all instruments will be available as a backup system in the event of technical difficulties with the electronic administration system.
2. Redcap allows for a secure portal to complete all study-related forms including all self-report questionnaires. These data are stored behind an encrypted firewall, and

automatically backed up. All database files will be password protected, and only study staff will have access to the study databases. Any paper data will be de-identified, and kept in the laboratory in a locked suite and cabinet.

3. Screening information from those individuals who after screening are deemed ineligible for the study or choose not to enroll will be completely de-identified and retained in encrypted form on Northwestern University's secure server, within password protected folders to which only study personnel will have access. During the screening process, only information which could be used to determine eligibility or schedule appointments is obtained. This information will not be used for research purposes, including data analysis. However, in order to track reasons for ineligibility and for reporting to our funding source, we will need to retain deidentified screening information. All individuals who engage in the screening process will be given an opportunity to allow us to re-contact them for future studies. We will not retain contact information for participants who opt-out of future contact. In order to accurately capture all reasons for ineligibility, protect the confidentiality of participants who have already enrolled in the project, and mitigate instances of multiple screening attempts by a single individual, potential participants will complete the full screening survey. An explanation has been added to the phone screen interview script, where potential participants will have an opportunity to discuss this with a member of the study team before continuing with the next step of the screening process.
4. All Data related to the study will be stored for 7 years after study completion, per Northwestern's IRB policy.
5. Only staff on the study personnel list registered with IRB will have access to study data and participant identifiers and study staff who will be accessing data will be trained on Good Clinical Practices to maintain confidentiality, data integrity, and basic data security measures.
6. The principal investigator, study coordinator, and data manager will be responsible for the transmission and receipt of all data.
7. All study assessments administered electronically will be designed to disallow invalid response values and to flag and alert study personnel to incomplete instruments prior to saving the data. The data will be visually checked by the data manager who will log in each assessment battery file for each participant. For paper data, all hand-computations will be double-checked and double entered. Web administered screening data and Smartphone data uploaded to the study server will be backed up each evening, and downloaded for local backup and storage with other study data. After checking for accuracy and completeness of each file, all electronic data will be backed up on the project manager's and data manager's computers, and backed up to a secure remote hard drive. All database files will be password protected, and only study staff will have access to staff computers or the secure remote hard drive. Paper data will be kept in the laboratory in a locked cabinet.
8. Data set transfer to the University of Michigan Investigators will be done either using secure file transfer protocol or physical transport of encrypted material. Before sharing data with the Michigan Investigators, data will be stripped of all personal identifiers and all identifying codes. Participants will not be identified in any public records or documents. Data will be stored on several geographically dispersed workstations at the University of Michigan's Institute for Social Research, each behind a secure firewall, and

password protected. All individuals with access to data have been trained on human subject protection.

17.0 Data Monitoring Plan to Ensure the Safety of Participants:

We propose a DSMP because of the benefits to the scientific integrity of the study as well as the protection of human participants. DSMP members will be independent of the investigators and comprise specialists in obesity treatment, clinical trials, and biostatistics who can oversee the study and offer guidance to the PI. The DSMP will have three voting members and two non-voting members. Drs. Spring (PI) and Nahum-Shani (PI) and Dr. Hedeker, project statistician, will be non-voting members of the DSMP. They will attend all meetings primarily to provide and receive information. The DSMP will convene in person or by telephone at least every six months. They will review all adverse events as well as data on study recruitment and retention. Study staff will inform the DSMP immediately if any participant is experiencing serious medical or psychiatric deterioration that is thought to be study-related. The appropriate member of the DSMP will evaluate or oversee the evaluation of the participant. If the patient is determined to have deteriorated, he or she will be referred for appropriate treatment and, if appropriate, discontinued from the study protocol. Baseline assessment will screen out study candidates who endorse active suicidality that could place them at risk in a weight loss trial. In the event a candidate endorses active suicidality (determined by their responses to the PHQ-9; Table 1), SMART study personnel will consult the suicidality protocol decision tree and follow all necessary reporting procedures. Northwestern University's Office for the Protection of Research Subjects and IRB will be contacted immediately about all serious adverse events that are thought to be study-related. Reports will be written immediately for all events deemed significant by the Northwestern University IRB; such reports will be provided to all DSMP members. DSMP members may also be called upon for advice in managing such problems. Reports from DSMP meetings will be given to the Northwestern University IRB and the NIH program officer. If there are any suspected signs of consistent adverse events, we will ask the Northwestern University IRB to assist in the appointment of an outside monitor to review data and protocols. Dr. Spring, the biostatistician, Co-I (Dr. Pfammatter) and project manager will also perform all necessary checks and controls to ensure the reliability and validity of the data, including monitoring data collection procedures, data storage, data management, and data analysis. Dr. Hedeker will provide the DSMP with a data report at each meeting.

18.0 Data, and if applicable, Specimen Banking:

No specimens will be collected for this particular study.

All data to be collected will be stored for 7 years according to Northwestern's IRB policies. Redcap and/or Study Tracker allow for a secure portal to complete all study-related forms including all self-report questionnaires. These data are stored behind an encrypted firewall, and automatically backed up. All database files will be password protected, and only study staff will have access to the study databases. Any paper data will be de-identified, and kept in the laboratory in a locked suite and cabinet.

19.0 Data Sharing:

Data set transfer will occur between Northwestern University and the University of Michigan for the purposes of data analysis. This transfer will be done either using secure file transfer protocol or physical transfer of encrypted material. Before sharing data with the Michigan Investigators,

data will be stripped of all personal identifiers and all identifying codes. Participants will not be identified in any public records or documents. Data will be stored on several geographically dispersed workstations at the University of Michigan's Institute for Social Research, each behind a secure firewall, and password protected. All individuals with access to data have been trained on human subject protection and will be under the supervision of Dr. Nahum-Shani.

Qualifications to Conduct Research and Resources Available:

Resources and Facilities

Clinical

The DPM's clinic space which is used for exams for several studies, occupies 10,184 square feet of space on the 14th floor of the 680 N. Lake Shore Drive building, and is in a suite that is connected to the administrative and faculty offices via a locked doorway. In addition to office and workstation space for clinic staff, the clinic includes 19 exam/interview rooms, a modern laboratory for processing biological specimens, a phlebotomy area with 3 stations for drawing blood (including one reclining chair), and 2 rooms for exercise assessment and training. The exam/interview rooms range in size from 100 square feet to 150 square feet and easily accommodate such items as an ultrasound machine and other large-sized equipment. In addition, the clinic offers a comfortable, open reception area; a conference room; a kitchen in which participant snacks are prepared; space for multiple file cabinets; and three private restrooms, one of which contains a shower. The proposed study will use the clinic space to complete assessments and to train participants on the use of the study's smartphone application. A balance beam scale, stadiometer, blood pressure machine, and computer will be stored and used within an exam/interview room which will allow the proposed study to conduct private, individual assessments at baseline, 3, 6, and 12 months.

Office

The non-clinic portion of the DPM occupies 19,076 sf square feet of office space on the 14th floor and 12,000 square feet on the 15th floor of 680 N. Lake Shore Drive, an office building directly across the street from the FSM campus. The Department is fully linked to all University services via the on-campus telephone system and hardwire computer networking services. Department space includes offices for all faculty and three separate rooms for fellows and students. The PI, Co-I and research staff have offices and cubicles located on the 15th floor, and the department has a private stairwell to quickly access the department clinic to meet participants in a timely manner.

Other

The DPM maintains its own Library with a full selection of journals in clinical psychology, public health, preventive medicine, and biostatistics. In addition, Northwestern is one of the country's leading private research universities and medical schools. The University libraries provide comprehensive resources and research services in every major field totaling more than 4.9 million volumes, 10th among the nations' private universities. Northwestern University Information Technology supports researchers with the software, hardware, and data storage and retrieval facilities to conduct large-scale projects. In addition, the proposed study will use NITRO Study Tracker, a secure, web-based clinical research tool to help improve efficiency, safety, and security for subjects in research studies. The research subject tracking log of NITRO

Study Tracker is used for all human clinical trials initiated by researchers at Northwestern University and Northwestern Medicine.

The DPM's facilities also include one large conference room that seats up to 60 people and four smaller conference rooms that seat up to 30 people for classes, seminars, and meetings. Conference rooms will be used for the current study to conduct large group orientation sessions, as well as smaller project staff meetings. A large demonstration kitchen is housed in departmental space and is available for conducting dietary intervention studies both for research staff and participants.

External Resources Available to Participants
External resource lists will be provided to participants who express need for further psychological support during their participation or for continued weight maintenance support following their participation. Resource lists will be similar to those used in other weight loss studies.

Staff Training
All persons who will be assisting with research will be required to complete CITI and GCP training as mandated by the university prior to accessing study-related materials. In addition staff reviews IRB peer education presentations prepared by the staff. A staff training protocol specifically for SMART has been developed to ensure all persons are adequately trained on all study protocols, procedures, duties, and functions. The training is outlined below:

Basic SMART Staff Training

1. The Project Coordinator will give a training binder to new staff and review binder sections with them. The Project Coordinator, Lab Manager or other experienced research staff will review participant protection and lab policies with new staff and coordinate their training.
2. New staff member will read study protocol and consent, phone screen and orientation SOP's, phone screen script and Orientation PowerPoint.
3. The Project Coordinator or experienced Research Assistant will review the study protocol with the new research assistant and answer questions.
4. The Project Coordinator or experienced Research Assistant will coordinate shadow experiences with Research Assistants, schedule phone screen practices and observe initial phone screen calls.
5. The Project Coordinator or experienced Research Assistant will also schedule times for new research assistant to observe and participate in Orientation sessions and schedule a practice presentation session in front of lab members and provide feedback on presentation.
6. The Project Coordinator or experienced Research Assistant will observe first presentation given by the new staff research assistant.
7. The Project Coordinator will assign the new Research Assistant to either an assessor or coach role.

SMART Coach Training

1. Employee new to coaching will be provided with all procedures relevant to coaching to read.
2. Employee new to coaching will read the motivational interviewing material and watch

the videos provided.
3. The Clinical Psychologist will schedule and teach the motivational interviewing course and oversee mock interviews.
4. The employee new to coaching will shadow experienced Coaches until they feel comfortable with the procedures.
5. The employee new to coaching will practice coaching calls with experienced Coaches.
6. The employee new to coaching will learn how to download and use the SMART and Fitbit apps, and view and practice the Randomization PowerPoint in preparation for randomization training.
7. An experienced Coach will demonstrate the Randomization procedures and the trainee will shadow Coaches while they Randomize participants.
8. When the trainee receives their first participant assignment, their Randomization and Coaching call will be observed by an experienced coach.

SMART Assessor Training

1. The Project Coordinator will arrange the initial training session with the Assessment Staff.
2. Staff members who will be conducting assessments will be provided with the assessment procedures and equipment manuals to read and reference.
3. Staff members who will be conducting assessments will take a post-test for each piece of equipment being used during the assessments. These post-tests will be kept in the Staff training binder with the Study Coordinator. Passing scores for post-test exams are 80%.
4. The written test will only be performed upon the initial training session. Refresher trainings will involve observation only.
5. Staff members who will be conducting assessments will be asked to perform the assessment procedures on five different volunteers under the observation of the designated trainer or study coordinator.
6. An experienced assessor will demonstrate assessment procedures.
7. The staff member being trained may observe assessment staff performing assessment.
8. The staff member being trained will practice the procedures before graded observation.
9. Each observed training episode will be documented on the anthropometric and blood pressure training checklists.
10. Feedback will be provided during the training session to verify or correct (if applicable) the staff member's performance as needed.
11. Staff members who will be conducting assessments will be asked to repeat the performance of the assessment procedures on the same five volunteers one week later. This also will be under the observation of the designated trainer or study coordinator.
12. If the repeat measurements are not within the designated allowances based on individual protocols the staff member will be asked to conduct the repetition again (one week apart) until the measurements fall within the designated allowance.
13. Furthermore, if the staff member does not follow the approved protocol for all checkpoints, the staff member will be asked to conduct the repetition again (one week apart) until the staff member follows the approved protocol as written at 100%.

14. The designated trainer or study coordinator will observe the first assessment with a participant performed by the new assessor.
15. Follow-up and refresher training will be completed every 6-months and as needed, respectively.
16. Refresher and Follow-up training sessions will be conducted on two volunteers rather than the initial five.

References

1. Moyer VA, Force USPST. Screening for and management of obesity in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. Sep 4 2012;157(5):373-8. doi:10.7326/0003-4819-157-5-201209040-00475
2. Leblanc ES, O'Connor E, Whitlock EP, Patnode CD, Kapka T. Effectiveness of primary care-relevant treatments for obesity in adults: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. Oct 4 2011;155(7):434-47. doi:10.7326/0003-4819-155-7-201110040-00006
3. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England journal of medicine*. 2002;346(6):393-403. doi:10.1056/NEJMoa012512
4. Look ARG, Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med*. Sep 27 2010;170(17):1566-75. doi:10.1001/archinternmed.2010.334
5. Richards DA, Bower P, Pagel C, et al. Delivering stepped care: an analysis of implementation in routine practice. *Implement Sci*. 2012;7:3. doi:10.1186/1748-5908-7-3
6. Excellence NIfHaC. Commissioning stepped care for people with common mental health disorders. 2015. http://www.nice.org.uk/guidance/cmg41
7. Jakicic JM, Tate DF, Lang W, et al. Effect of a stepped-care intervention approach on weight loss in adults: a randomized clinical trial. *JAMA*. Jun 27 2012;307(24):2617-26. doi:10.1001/jama.2012.6866
8. Bower P, Gilbody S. Stepped care in psychological therapies: access, effectiveness and efficiency. Narrative literature review. *Br J Psychiatry*. Jan 2005;186:11-7. doi:10.1192/bjp.186.1.11
9. Turpin G, Richards D, Hope R, Duffy R. Improving access to psychological therapies in a national initiative to ensure the delivery of high qualiity evidence-based therapies. *Papeles del Psicologo*. 2008;29(3)
10. Carels RA, Darby L, Cacciapaglia HM, et al. Applying a stepped-care approach to the treatment of obesity. *J Psychosom Res*. Dec 2005;59(6):375-83. doi:10.1016/j.jpsychores.2005.06.060
11. Carels RA, Darby L, Cacciapaglia HM, et al. Using motivational interviewing as a supplement to obesity treatment: a stepped-care approach. *Health Psychol*. May 2007;26(3):369-74. doi:10.1037/0278-6133.26.3.369
12. Collins LM, Murphy SA, Bierman KL. A conceptual framework for adaptive preventive interventions. *Prev Sci*. Sep 2004;5(3):185-96.
13. Lei H, Nahum-Shani I, Lynch K, Oslin D, Murphy SA. A "SMART" design for building individualized treatment sequences. *Annu Rev Clin Psychol*. 2012;8:21-48. doi:10.1146/annurev-clinpsy-032511-143152
14. Murphy SA. An experimental design for the development of adaptive treatment strategies. *Stat Med*. May 30 2005;24(10):1455-81. doi:10.1002/sim.2022
15. Unick JL, Hogan PE, Neiberg RH, et al. Evaluation of early weight loss thresholds for identifying nonresponders to an intensive lifestyle intervention. *Obesity (Silver Spring)*. Jul 2014;22(7):1608-16. doi:10.1002/oby.20777
16. Unick JL, Neiberg RH, Hogan PE, et al. Weight change in the first 2 months of a lifestyle intervention predicts weight changes 8 years later. *Obesity (Silver Spring)*. Jul 2015;23(7):1353-6. doi:10.1002/oby.21112
17. Pellegrini CA, Duncan JM, Moller AC, et al. A smartphone-supported weight loss program: design of the ENGAGED randomized controlled trial. *BMC Public Health*. Nov 30 2012;12(1):1041. doi:10.1186/1471-2458-12-1041
18. Deci EL, Ryan RM. The "What" and "Why" of Goal Pursuits: Human Needs and Self-Determination of Behavior. *Psychological Inquiry*. 2000;11(4):227-268.
19. WHITE RW. Motivation reconsidered: the concept of competence. *Psychol Rev*. Sep 1959;66:297-333.

doi:10.1037/h0040934
20. Varvel SJ, He Y, Shannon JK, et al. Multidimensional, threshold effects of social support in firefighters: Is more support invariably better? *Journal of Counseling Psychology*. 2007;54(4):458–465. doi:https://doi.org/10.1037/0022-0167.54.4.458
21. Mallinckrodt B, Armer JM, Heppner PP. A threshold model of social support, adjustment, and distress after breast cancer treatment. *J Couns Psychol*. Jan 2012;59(1):150-60. doi:10.1037/a0026549
22. Nahum-Shani I, Qian M, Almirall D, et al. Experimental design and primary data analysis methods for comparing adaptive interventions. *Psychol Methods*. Dec 2012;17(4):457-77. doi:10.1037/a0029372
23. Nahum-Shani I, Qian M, Almirall D, et al. Q-learning: a data analysis method for constructing adaptive interventions. *Psychol Methods*. Dec 2012;17(4):478-94. doi:10.1037/a0029373
24. Scott NW, McPherson GC, Ramsay CR, Campbell MK. The method of minimization for allocation to clinical trials. a review. *Control Clin Trials*. Dec 2002;23(6):662-74. doi:https://doi.org/10.1016/s0197-2456(02)00242-8
25. Taves DR. Minimization: a new method of assigning patients to treatment and control groups. *Clin Pharmacol Ther*. May 1974;15(5):443-53. doi:https://doi.org/10.1002/cpt1974155443
26. Goldberg JH, Kiernan M. Innovative techniques to address retention in a behavioral weight-loss trial.
Clinical Trial
Randomized Controlled Trial
Research Support, N.I.H., Extramural
Research Support, U.S. Gov't, P.H.S. *Health Educ Res*. Aug 2005;20(4):439-47. doi:10.1093/her/cyg139
27. Thomas S, Reading J, Shephard RJ. Revision of the Physical Activity Readiness Questionnaire (PAR-Q). *Can J Sport Sci*. Dec 1992;17(4):338-45.
28. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA*. Nov 10 1999;282(18):1737-44. doi:https://doi.org/10.1001/jama.282.18.1737
29. Feldman PJ, Steptoe A. Psychosocial and socioeconomic factors associated with glycated hemoglobin in nondiabetic middle-aged men and women. *Health Psychol*. Jul 2003;22(4):398-405. doi:10.1037/0278-6133.22.4.398
30. Stich C, Knauper B, Tint A. A scenario-based dieting self-efficacy scale: the DIET-SE. *Assessment*. Mar 2009;16(1):16-30. doi:10.1177/1073191108322000
31. Marcus BH, Selby VC, Niaura RS, Rossi JS. Self-efficacy and the stages of exercise behavior change. *Res Q Exerc Sport*. Mar 1992;63(1):60-6. doi:https://doi.org/10.1080/02701367.1992.10607557
32. Williams GC, Grow VM, Freedman ZR, Ryan RM, Deci EL. Motivational predictors of weight loss and weight-loss maintenance. *J Pers Soc Psychol*. Jan 1996;70(1):115-26. doi:https://doi.org/10.1037//0022-3514.70.1.115
33. Vinkers CD, Adriaanse MA, de Ridder DT. In it for the long haul: characteristics of early and late drop out in a self-management intervention for weight control. *J Behav Med*. Oct 2013;36(5):520-30. doi:10.1007/s10865-012-9446-9
34. Ritzwoller DP, Sukhanova A, Gaglio B, Glasgow RE. Costing behavioral interventions: a practical guide to enhance translation. *Ann Behav Med*. Apr 2009;37(2):218-27. doi:10.1007/s12160-009-9088-5
35. Group. E. EQ-5G: A standardized instrument for use as a measure of health outcomes. Accessed January 29, 2014. http://www.euroqol.org/.
36. Hagberg LA, Brekke HK, Bertz F, Winkvist A. Cost-utility analysis of a randomized controlled weight loss trial among lactating overweight/obese women. *BMC Public Health*. Jan 15 2014;14(1):38. doi:10.1186/1471-2458-14-38
37. Jennrich RI, Schluchter MD. Unbalanced repeated-measures models with structured covariance matrices. *Biometrics*. Dec 1986;42(4):805-20.
38. Laird NM. Missing data in longitudinal studies. *Stat Med*. 1988;7(1-2):305-15. doi:10.1002/sim.4780070131
39. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods*. Jun 2013;18(2):137-50. doi:10.1037/a0031034
40. Fritz MS, Mackinnon DP. Required sample size to detect the mediated effect. *Psychol Sci*. Mar

2007;18(3):233-9. doi:10.1111/j.1467-9280.2007.01882.x
41. Murphy SA, Collins LM, Rush AJ. Customizing treatment to the patient: adaptive treatment strategies. *Drug Alcohol Depend*. May 2007;88 Suppl 2:S1-3. doi:10.1016/j.drugalcdep.2007.02.001
42. MacKinnon D. *Introduction to statistical mediation analysis*. Lawrence Erlbaum Associates; 2008.
43. Orellana L, Rotnitzky A, Robins JM. Dynamic regime marginal structural mean models for estimation of optimal dynamic treatment regimes, Part I: main content. *Int J Biostat*. 2010;6(2):Article 8.
44. Robins J, Orellana L, Rotnitzky A. Estimation and extrapolation of optimal treatment and testing strategies. *Stat Med*. Oct 15 2008;27(23):4678-721. doi:10.1002/sim.3301
45. Liang KY, Zeger SL. Longitudinal data analysis using geralized linear models. *Biometrika*. 1986;73(1):13-22.
46. Ramsey SD, Willke RJ, Glick H, et al. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. *Value Health*. Mar 2015;18(2):161-72. doi:10.1016/j.jval.2015.02.001
47. O'Brien BJ, Drummond MF, Labelle RJ, Willan A. In search of power and significance: issues in the design and analysis of stochastic cost-effectiveness studies in health care. *Med Care*. Feb 1994;32(2):150-63. doi:https://doi.org/10.1097/00005650-199402000-00006
48. Molenberghs G, Kenward MG. *Missing data in clinical studies*. Wiley & Sons; 2007.
49. Hedeker D, Gibbons RD. *Longitudinal data analysis*. vol 451. John Wiley & Sons; 2006.
50. Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. *BMJ*. Jul 06 1996;313(7048):36-9. doi:10.1136/bmj.313.7048.36
51. Thomas JG, Bond DS, Raynor HA, Papandonatos GD, Wing RR. Comparison of Smartphone-Based Behavioral Obesity Treatment With Gold Standard Group Treatment and Control: A Randomized Trial. *Obesity (Silver Spring)*. Apr 2019;27(4):572-580. doi:10.1002/oby.22410
52. Wieland LS, Falzon L, Sciamanna CN, et al. Interactive computer-based interventions for weight loss or weight maintenance in overweight or obese people. *Cochrane Database Syst Rev*. 2012;8:CD007675. doi:10.1002/14651858.CD007675.pub2
53. Spring B, Duncan JM, Janke EA, et al. Integrating technology into standard weight loss treatment: a randomized controlled trial. *JAMA Intern Med*. Jan 2013;173(2):105-11. doi:10.1001/jamainternmed.2013.1221

Protocol Document History

Original Protocol – December 01, 2015			
Amendment 1, Version 2 – December 01, 2015 **IRB Modification Number: MOD0001** ***Approved by IRB:*** **December 01, 2015**			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
1.0, 4.0, 8.1, 9.0, 12.0, 13.2,	Version 1	Added language throughout the protocol to reflect that this protocol is still a JIT request, and that a few components of participant payment, funding, etc. will be updated after award is fully funded	This protocol is still a JIT request, and a few components of participant payment, funding, etc. will be updated after the award is fully funded. The language changes make it clearer what will be determined later
Amendment 2, Version 3 – September 2, 2016 **IRB Modification Number: MOD0007** ***Approved by IRB: November 7, 2016***			
Section(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***

1.2, 2.1, 3.0, 4.0, 4.4, 4.6, 7.1, 7.2, 8.0, 10.0, 12.0, 14.0, 15.0	Version 2	Updated funding info. Removed JIT info. Moved Aims to their own section (1.2 now). 2.0 - Updated inclusion to add info about the inclusion of women and minorities. Added inclusion: weight stable over last 6 months, not taking weight loss meds, interested in losing weight, and live in Chicago area. 3.0 - For exclusion, added unstable medical conditions, binge eating, anything preventing mod PA, pacemaker, bariatric surgery, participants living together. 4.0 – updated setting to DPM, updated study design to better explain the different step-up conditions. Added the Wireless Scale section, added the Wireless Accelerometer section, added the SMART App section, added the Online Lessons section, re-ordered the Telephone Coaching (APP+C), Augmentation Tactics, MR< and Text sections. 4.4 – Added the following headings and information: Web Screening, Telephone Screening, In-Person Group Orientation, Pre-baseline Session at-home Activities,	Study has been funded since receiving initial approval, so updated our previous "TBD" funding info. Pulled Aims into own section to better fit IRB template guide. Also added a lot more detail to many sections of the protocol now that funding has been received and the study team has thought through many more details.
		Randomization, Tech Training, Online Questionnaires, In-Person Assessment Sessions, Exit Interview, Result Session, and Assessment Only Participants. Also added locator people 4.6 – Added more detail about our screening tools – names the measures 7.1 added some recruitment strategies – flyers, websites, IWHR, research match, health fairs, CTA 7.2 added that we will have a bi-weekly progress meeting with study team 8.0 – added to consent process that we will ask about optional audio recording, and contact about future studies 10.0 – added 3 and 4 to risk of participating, and info about participant's rights to discontinue the study at any time for any reason 12.0 put in real amounts of financial compensation 14.0 – updated our data storage to say all is kept on NU encrypted and secure server 15.0 – noted that those who endorse suicidality will be excluded	
Amendment 3, Version 4 – December 16, 2016 **IRB Modification Number: MOD0009** ***Approved by IRB: January 4, 2017***			

Section(s) Affected	*Prior Version*	*Amendment 3 Changes*	*Rationale*
4.2, 4.6, 7.1, 10.0	Version 3	4.2 – Online Lessons – added that participants will login with a user id and password. SMART App – added that participants will complete a value-sort task. Text Messages – added timing of the messages at wake time, midday, and evening. Tech Training – added that participants will set a wake and sleep time in the app. 4.6 - Cost-Effectiveness – added that we will measure absenteeism and presenteeism at each assessment timepoint. 7.1. – Recruitment Strategies – added that we will contact former participants who agreed to be contacted for other studies 10.0. – added a note that if BP is elevated, we may get physician approval to participate, and if dangerously elevated we will dial 911	Now that the app is being created, we now know they will login. Recently added measures of cost effectiveness, recently added the BP elevation

Amendment 4, Version 5 - March 14, 2017
IRB Modification Number*:* MOD0012
Approved by IRB: May 11, 2017

Section(s) Affected	*Prior Version*	*Amendment 4 Changes*	*Rationale*
2.0, 3.2, 4.2, 4.3, 4.4, 4.7. 7.1, 8.0, 15.0, 17.0	Version 4	2.0 – added note that re-rand is at beginning of 3rd week 3.2 – added that need internet for 6 months to list of inclusion criteria 4.2 – added more detail about re-randomization timing happening at beginning of 3rd week 4.3. – added more detail to convey that meal replacements are to replace 2 meals per day 4.4 added will mail participants a letter to retain if other contact methods have failed 4.7 – Made clear that randomization fidelity and app use fidelity are tracked along with call fidelity 7.1 – added explicit mention of clinicaltrials.gov as a recruitment channel 8.0 – added equipoise induction in an orientation session 15.0 – changes name of DSMB to DSMP 17.0 – added what training our assessors and coaches undergo before working with participants – training binder, scheduling practice sessions, clinical psychologist overview, etc.	Added more detail to a few sections

Amendment 5, Version 6 - May 19, 2017 **IRB Modification Number*:* MOD0014** ***Approved by IRB: May 31, 2017***			
Section(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
3.0, 17.0	Version 5	3.0 – added not using MR to eligibility criteria, and that anyone who was in one of our other studies must wait 3 months until participating in this trial 17.0 – Noted for staff refresher training, only need to practice on two volunteers rather than 5	Need to update eligibility so that if participants are already taking MR they are IE, as if they ended up in a non-MR condition that would bias results. Also lowered practice session amount for refresher training as 5 was too many practice attempts and were extraneous
Amendment 6, Version 7 - July 24, 2017 **IRB Modification Number*:* MOD0018** ***Approved by IRB: July 25, 2017***			
Section(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
3.0	Version 6	3.0 – added to exclusion criteria anyone who seems unwilling or unable to complete study procedures	Have had some participants express in pre-randomization calls not wanting to be randomized to certain conditions, or saying they will not follow procedures, so we want to be able to exclude them before randomization
Amendment 7, Version 8 - July 28, 2017 **IRB Modification Number*:* MOD0020** ***Approved by IRB: August 1, 2017***			
Section(s) Affected	***Prior Version***	***Amendment 7 Changes***	***Rationale***

4.0	Version 7	Added that participants who are not randomized to coaching calls and do not record anything in the APP for one week will be called by a staff RA. After the first 8 weeks of the intervention, the participant will be called if there are 2 weeks of no APP activity	Goal of this modification is to increase study retention and prevent drop-out
Amendment 8, Version 9 – August 4, 2017 **IRB Modification Number*:* MOD0021** ***Approved by IRB: August 15, 2017***			
Section(s) Affected	***Prior Version***	***Amendment 8 Changes***	***Rationale***
3.0	Version 8	Added an exclusion that if study candidate was found to be non-adherent or dropped out in a previous study with our group, we would exclude	Attempt to increase study retention and prevent drop-out by excluding before randomization anyone we do not think will adhere to or complete our protocol
Amendment 9, Version 10 – September 21, 2017 **IRB Modification Number*:* MOD0024** ***Approved by IRB: September 25, 2017***			
Section(s) Affected	***Prior Version***	***Amendment 9 Changes***	***Rationale***
4.0	Version 9	If the study is experiencing a high volume of participants and is nearing capacity, eligible candidates will receive an email notifying them that we will reach out in the near future to schedule their phone screen.	Needed to account for overwhelming volume of potential participants
Amendment 10, Version 11 – September 26, 2017 **IRB Modification Number*:* MOD0025** ***Approved by IRB: October 6, 2017***			
Section(s) Affected	***Prior Version***	***Amendment 10 Changes***	***Rationale***

4.0, 8.0, 9.0	Version 10	4.0 – Follow-Up Health Assessments – we added our estimated length of time for completion of the follow-up visits and added that if participants miss their visit we will contact them by phone as well, not just via email. 8.0 & 9.0 – We have added a section about an addendum consent, as we changed our estimated length of study visit time on the consent form	We realized our follow-up visits were taking longer than initially estimated, so we changed our time length in the protocol and the consent. Since we changed the consent, we have created an addendum consent
Amendment 11, Version 12 – October 31, 2017 **IRB Modification Number*: MOD0028*** ***Approved by IRB: December 11, 2017***			
Section(s) Affected	***Prior Version***	***Amendment 11 Changes***	***Rationale***
Title Page, 5.0, 14.0	Version 11	Title Page – added ClinicalTrials.gov registration number 5.0 – added U Mich as a site, so needed to complete the multiple sites section 14.0 – added info on data transfer to UMich	Needed to add NCT# for federal compliance, needed to add UMich as a study site (with NU staying as IRB of record)
Amendment 12, Version 13 – February 15, 2018 **IRB Modification Number*: MOD0033*** ***Approved by IRB: April 23, 2018***			
Section(s) Affected	***Prior Version***	***Amendment 12 Changes***	***Rationale***
All	Version 12	Added Sensor Supplement	We were awarded a supplement to study the addition of HealBe and bioribbon passive-sensing systems to participants for 2 weeks of their time in the trial, to assess biomarkers
			indicators of treatment response. We added information about the supplement procedures throughout our protocol
Amendment 13, Version 14 – June 19, 2018 **IRB Modification Number*: MOD0043*** ***Approved by IRB: July 12, 2018***			
Section(s) Affected	***Prior Version***	***Amendment 13 Changes***	***Rationale***

8.0	Version 13	8.0 Tech Training – added a randomization checklist for study participants so they can track their upcoming visits and remaining study steps and added the same type of checklist for the supplement. The SMART App – made explicit note that the app will be provided during the tech training and will be able to use the app post-completion, and that by doing so they are giving permission for us to collect the data. Actigraph – noted that participants will be asked to note the time of day that they switch the actigraph from their wrist to waist and vise-versa	A checklist will allow participants to stay better informed about their next steps in the study. For the app, participants wanted the ability to keep using the app once their time in the study is over. We have added to the protocol and consent that by doing so, they are consenting to us continuing to receive their app data
Amendment 14, Version 15 – July 12, 2018 **IRB Modification Number*:* MOD0045** ***Approved by IRB: August 30, 2018***			
Section(s) Affected	***Prior Version***	***Amendment 14 Changes***	***Rationale***
1.0, 8.0, 15.0, 16.0	Version 14	1.0, 8.0, 16.0– changed healbe to dexcom. Removed Healbe instructions in 4.0 and added DexCom instructions 15.0 – added 2 risks related to DexCom – pain from insertion, small chance of fracturing of DexCom component under skin. Added statement that DexCom has been approved by FDA	Due to frequent malfunctioning, Healbe is no longer the device we will use for the supplement. We are partnering with DexCom instead, so changing HealhBe to Dexcom throughout protocol
Amendment 15, Version 16 – October 24, 2018 **IRB Modification Number*:* MOD0050** ***Approved by IRB: November 21, 2018***			
Section(s) Affected	***Prior Version***	***Amendment 15 Changes***	***Rationale***
8.0, 12.0	Version 15	Study retention – increase compensation from $20 per visit to $20 for 3mo, $40 for 6mo, $60 for 12 months.	Improve study retention
Amendment 16, Version 17 – April 12, 2019 **IRB Modification Number*:* 000MOD58** ***Approved by IRB: June 5, 2019***			
Section(s) Affected	***Prior Version***	***Amendment 16 Changes***	***Rationale***
8.0	Version 16	8.0 study retention plan – added that we will send appointment reminder cards, birthday cards, and that to maintain confidentiality they will be mailed in a sealed envelope with no study-specific identifiers	Improve retention

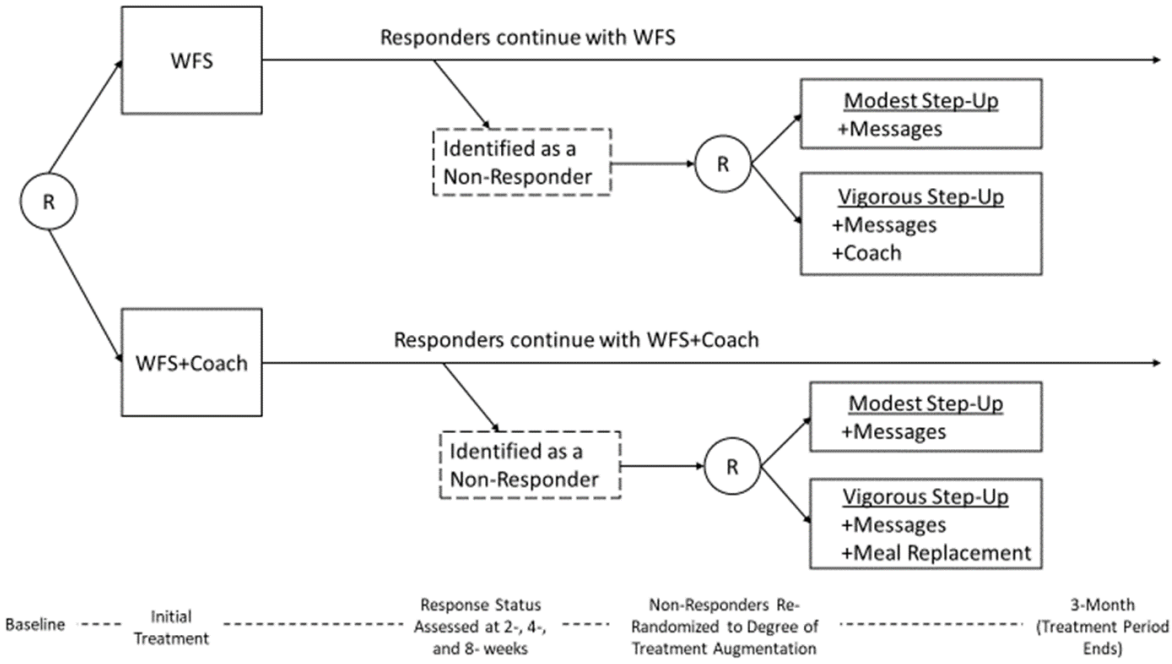
Amendment 17, Version 18 – August 26, 2018 **IRB Modification Number*:* MOD0064** ***Approved by IRB: September 1, 2018***			
Section(s) Affected	***Prior Version***	***Amendment 17 Changes***	
8.0	Version 17	Study retention – added a newsletter	To improve retention
Amendment 18, Version 19 – March 12, 2020 **IRB Modification Number*:* MOD0069** ***Approved by IRB: March 19, 2020***			
Section(s) Affected	***Prior Version***	***Amendment 18 Changes***	
8.0, 12.0	Version 18	8.0 - Added remote assessments as an option rather than in-person assessments 12.0 – Added that if complete assessments remotely, will be paid via online stored value card rather than cash	Due to Covid-19, we are switching to remote assessments rather than in-person to protect the health of our participants our staff
Amendment 19, Version 20 **March 20, 2020**			
Section(s) Affected	***Prior Version***	***Amendment 19 Changes***	
8.0	Version 20	Statistical Analysis: 1) Removal of BMI as a covariate in models of weight change 2) Change from a linear mixed-effects longitudinal model to a covariance pattern model (CPM) and a change from using SAS to SPSS for the Primary Aim 1 analysis, the month 12 analysis, and the analysis of sensitivity to missing data assumptions 3) Use of a counterfactual framework for assessing mediation rather than the use of marginal structural models 4) Month 12 analysis. Switch to CPM. Replace Proc Mixed with SPSS.	Rationale: 1) Because baseline weight was the first repeated measure in the longitudinal analysis, which was highly correlated with baseline BMI (especially with sex included as a covariate), including baseline BMI as a covariate led to computational issues that compromised the longitudinal analysis. 2) The CPM, using time indicators with baseline as the reference, was better

			suited to the study aims (i.e., weight changes at follow-ups), and allowed for a general variance-covariance structure. 3) We determined that the counterfactual framework is more appropriate for a clinical trial. 4) Month 12 was included as the last timepoint in the CPM, and was performed using SPSS MIXED because the data analyst was more familiar with SPSS than SAS
Amendment 20, Version 21 October 12, 2023			
Section(s) Affected	***Prior Version***	***Amendment 20 Changes***	
All	Version 19	Changed the name of components from "APP" (app) to "WFS" (wireless feedback system) to be more precise about what tools participants receive	Wireless feedback system more clearly explains what participants received as part of the intervention

Supplement 2 – Supplementary Figures and Tables

eFigure 1

Research Design



WFS = Wireless feedback system
WFS+C = Wireless feedback system + coaching
R = randomization

Participants were initially randomized to WFS versus WFS+C.

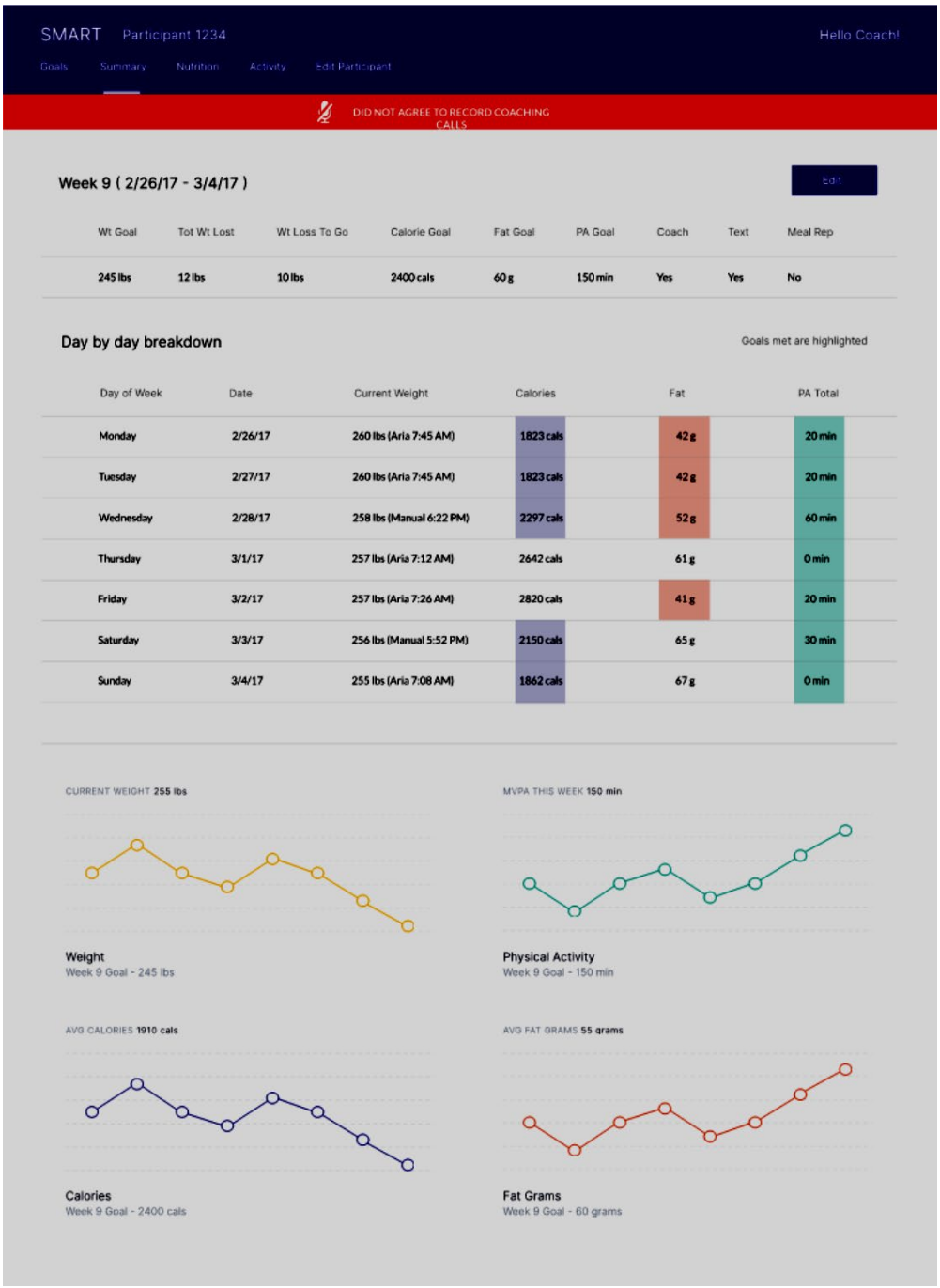
Nonresponders (< 0.23 kg weight loss per week) at 2, 4, or 8 week follow-up were re-randomized to modest (low resource-intensive) step-up comprising supportive messaging via mobile device push notifications [app-based screen alerts] versus vigorous (more resource-intensive) step-up comprising messaging with additional coaching or meal replacement.

Messaging was considered modest step-up for nonresponders to either initial treatment because it used few resources, and neither group had previously received it.

Vigorous step-up differs depending upon initial treatment because one first line treatment group, but not the other, has already received a resource-intensive traditional weight loss component (coaching) as initial treatment. For that group, coaching continued, rather than representing a step-up in intensity.

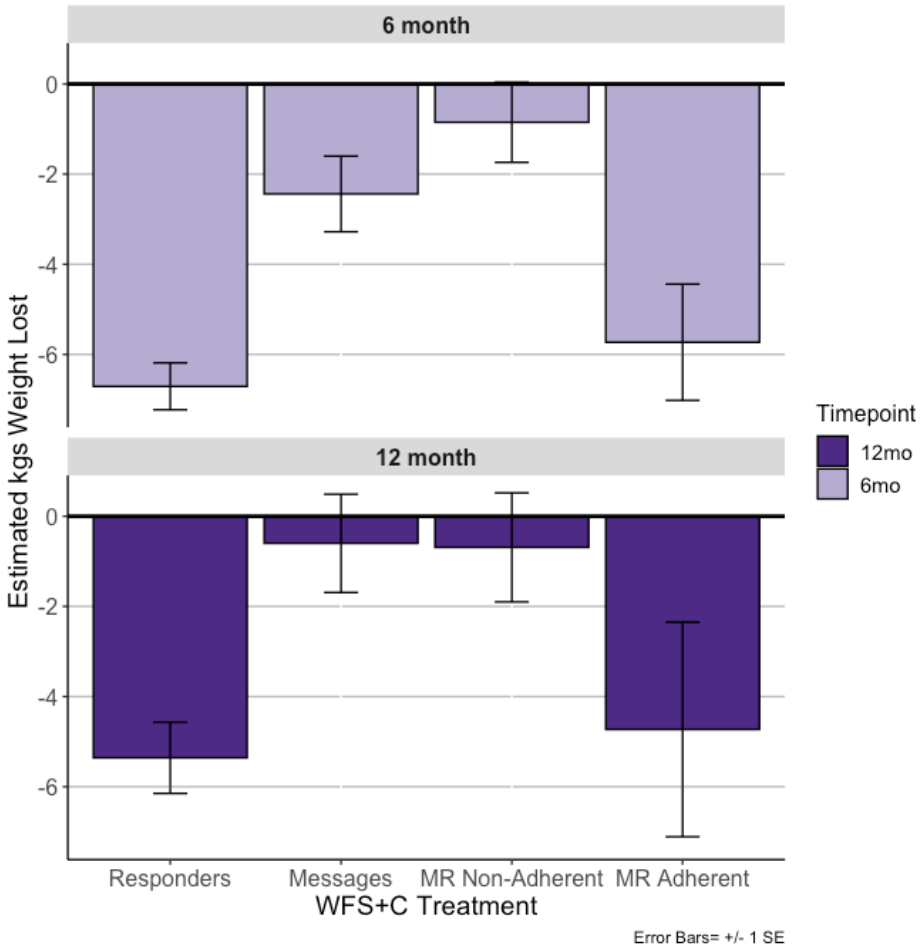
eFigure 2

WFS Health Promotionist Coach Dashboard



eFigure 3

Weight Loss for Participants with WFS+C as Initial Treatment



WFS+C = Wireless feedback system + coaching
MR = Meal replacement

Error bars = ± 1 standard error (SE)

Among 201 participants randomized to WFS+C, 108 (53.7%) responded. Non-responders to WFS + C (n=93) were re-randomized to WFS + C with supportive messaging alone or with meal replacement.

At both 6 and 12 month follow-ups, weight loss among the 50% of nonresponders who were 80% adherent to the replacement diet (i.e., they ate MR for ≥1 meal/day on 80% of days) approached that of initial responders.

By contrast, when WFS was first line treatment, no step-up tactic produced catch-up weight loss. Regardless of whether they received modest or vigorous step up, those treated initially with WFS failed to achieve even a 2 lb weight loss by 3 months, losing only 15% as much weight as treatment responders (data not shown).

eTable 1

M(SD) Weight, M(95%CI) Weight Change (kg) and Difference Between Modest Versus Vigorous Step-Up for Non-responders to Initial WFS vs. WFS+C*

	WFS (n=100)			WFS+C (n=93)			
Time	Baseline (kg)	Follow up (kg)	Weight change (kg) (95% CI)	Baseline (kg)	Follow up (kg)	Weight change (kg) (95% CI)	Between-Treatment Difference (kg) (95% CI)
Modest Step-up	n=47			n=49			
3 Months	97.1 (17.0)	96.5 (17.6)	-0.8 (-1.6, -0.1)	95.3 (15.8)	91.9 (15.8)	-2.3 (-3.4, -1.2)	-1.5 (-2.7 to -0.2)
6 Months	97.1 (17.0)	97.2 (18.0)	-0.6 (-1.6, 0.5)	95.3 (15.8)	92.0 (14.5)	-2.4 (-4.1, -0.8)	-1.9 (-3.8 to -0.0)
12 Months	97.1 (17.0)	97.0 (17.4)	-0.2 (-1.5, 1.1)	95.3 (15.8)	94.8 (16.7)	-0.6 (-2.8, 1.6)	-0.4 (-3.1 to 2.3)
Vigorous Step-up	n=53			n=44			
3 Months	94.7 (13.0)	92.3 (12.1)	-0.9 (-1.5, -0.2)	98.4 (16.9)	94.4 (17.1)	-3.2 (-4.3, -2.0)	-2.3 (-3.6 to -1.1)
6 Months	94.7 (13.0)	93.7 (12.7)	-0.6 (-1.7, 0.5)	98.4 (16.9)	94.9 (18.2)	-3.1 (-4.6, -1.5)	-2.5 (-4.4 to -0.6)
12 Months	94.7 (13.0)	94.2 (11.6)	0.1 (-1.8, 1.9)	98.4 (16.9)	96.6 (18.2)	-2.4 (-4.9, 0.0)	-2.5 (-5.2 to 0.2)

*n for above cells may be seen in Figure 1

Table e2

Mean weight change By Treatment Sequence*

	TS 1[a]	TS 2[b]	TS 3[c]	TS 4[d]	P-value for difference
Month 3	-2.7 (-5.1, -0.3)	-4.4 (-6.4, -2.4)	-5.2 (-7.2, -3.1)	-4.4 (-6.7, -2.1)	0.56
Month 6	-2.6 (-5.2, -0.0)	-4.1 (-6.3, -2.0)	-5.3 (-7.6, -3.1)	-4.3 (-6.9, -1.8)	0.57
Month 12	-1.9 (-4.6, 0.7)	-3.1 (-5.4, -0.8)	-3.3 (-6.0, -0.7)	-2.7 (-5.4, 0.1)	0.87

* Estimates are weight change (kg) (95% CI). Estimated means and 95% CIs were calculated using the weight and replicate method[36,37]. P-values in the last column are based on an overall (3 degrees of freedom) test of whether any of the embedded treatment sequences are different from one another at that follow up assessment.
TS = Treatment sequence
WFS = Wireless feedback system
WFS+C = Wireless feedback system + coaching

a: Initial: WFS alone. Responders continue with WFS alone, non-responders receive modest step-up.
b: Initial: WFS alone. Responders continue with WFS alone, non-responders receive vigorous step-up.
c: Initial: WFS+C. Responders continue with WFS+C, non-responders receive modest step-up.
d: Initial: WFS+C. Responders continue with WFS+C, non-responders receive vigorous step-up.
See Methods text and eFigure 1 (this Supplement) for details.

eTable 3
Median (95%CI) Within group Weight Change (kg) by Initial Treatment, and Difference Between Treatments

	WSF			WSF+C					
	Median Within grp Wt change (kg) at 6 Months (95%CI)	Test statistic	P value	Median Within grp Wt change (kg) at 6 Months (95%CI)	Test statistic	P value	Median Between-Treatment Wt change (kg) Difference at 6 Months	Test statistic	P value
Sex									
Male	-4.59 (-6.35, -2.72)	-3.31[1]	<.001	-6.58 (-7.71, -4.20)	-2.39[1]	.017	1.99	-1.03[1]	.305
Female	-1.59 (-2.15, 0.79)			-4.08 (-5.33, -3.06)			2.99	-3.79[1]	<.001
Age									
Younger (≤40)	-0.96 (-2.15, -0.68)	2.71[1]	.007	-3.86 (-5.33, -2.27)	1.37[1]	.169	2.90	-2.91[1]	.004
Older (>40)	-2.72 (-3.29, -1.81)			-5.33 (-6.01, -3.86)			2.61	-2.31[1]	.021
Race/Ethnicity									
White	-2.67 (-3.18, -1.59)	8.43[2]	.015	-5.67 (-6.58, -4.42)	11.27[2]	.004	3.00	-3.91[1]	<.001
Black	-1.36 (-2.04, 0.23)			-2.27 (-3.29, -0.57)			0.91	-1.29[1]	.199
Other	-0.57 (-1.13, 3.52)			-2.95 (-4.08, 0.00)			2.38	-1.35[1]	.186
Race/Eth Pairwise Comparisons*									
White-Black		-1.83[1]	.203		-2.79[1]	.016			
White-Other		-2.50[1]	.038		-2.32[1]	.062			
Black-Other		-1.00[1]	.946		-0.36[1]	1.000			

[1]Mann-Whitney, z [2]Kruskal-Wallace, H *All pairwise comparison P values are Bonferroni corrected

eTable 4

Mediation of Weight Loss Difference by Self-Monitoring, Self-Efficacy, and Autonomous Motivation *

Mediator	WFS	WFS+C	Difference (95% CI)[a]	Natural Direct Effect[b]	Natural Indirect Effect[c]	Proportion Mediated (95% CI)[d]
Proportion of days self-monitoring diet	0.60	0.69	0.09 (0.04, 0.14)	0.81	0.71	0.43 (0.22, 0.77)
Proportion of days self-monitoring weight	0.72	0.80	0.07 (0.03, 0.12)	1.18	0.48	0.29 (0.12, 0.57)
Proportion of days wearing the Fitbit	0.78	0.83	0.05 (-0.00, 0.10)	1.41	0.21	0.13 (-0.00, 0.31)
Diet self-efficacy change from baseline (mean) [e]	0.24	0.46	0.21 (0.04, 0.39)	1.45	0.22	0.14 (0.03, 0.32)
Exercise self-efficacy change from baseline (mean) [f]	-0.13	0.09	0.22 (0.03, 0.41)	1.46	0.18	0.11 (0.01, 0.29)
Autonomous motivation change from baseline (mean) [g]	-0.15	0.36	0.51 (0.25, 0.78)	1.20	0.42	0.26 (0.12, 0.51)

* Difference in variables between WFS vs WFS+C participants at 3 months

WFS = Wireless feedback system
WFS+C = Wireless feedback system + coaching

a: Absolute difference in mediator
b: Treatment effect on weight loss at a fixed level of the mediating variable.
c: Treatment effect on weight loss through effects on the mediating variable.
d. Proportion of treatment effect explained by changes in the mediating variable, defined as the natural indirect effect divided by the treatment effect. Confidence intervals obtained using a bias-corrected bootstrap with 5000 bootstrap samples. Interpretation: Greater self-monitoring of diet among WFS+C participants explained 43% of their greater 3-month weight loss vs WFS (differential treatment efficacy); greater self-monitoring of weight explained 29% of differential treatment efficacy; increases in measures of diet and exercise self-efficacy explained 11 and

14% of differential treatment efficacy respectively; and increases in autonomous motivation accounted for 26% of differential treatment efficacy.
e. Based on the 11-item Diet Self-Efficacy scale (DIET-SE), which measured confidence about maintaining eating self-control using 5-point Likert scales, where higher scores indicate greater self-efficacy. Measured at baseline and 3 months.
f. Based on the 18-item Physical Activity Self-Efficacy Scale, which measured confidence about being physically active using 5-point Likert scales, where higher scores indicate greater self-efficacy. Measured at baseline and 3 months.
g. Based on the abbreviated 4-item version of the Treatment Self-Regulation Questionnaire (TSRQ), which assessed autonomous motivation on 5-point scales, where higher scores indicated greater autonomous motivation. Measured at baseline and 3 months.

Supplement 3 – SMART Treatment Fidelity Checklists

1. Treatment: WFS Only

Date of Review:

Reviewer:

Coach:

Participant ID:

Participant Week:

Condition/components:

- Is the participant recording in the APP? (Y/N) Y = 1, N=1
  - If no: MIA protocol followed? (Y/N) Y=1
- Was participant re-randomized? (Y/N) Y=0, N=1
  - Did the re-randomization occur per protocol? (Y/N) Y=1
- Was the participant supposed to be re-randomized? (Y/N) Congruent with prior question = 1
  - Which week? (1-12)
  - Why? (Nonresponder/MIA)
  - Were the re-randomization details tracked in the "Randomization Tracking" form in the "SMART Randomization and Coaching" project? (Y/N) Y=1

SCORING: */5 (if re-randomized)
*/3 (if not re-randomized)

*WFS:	Wireless Feedback System
Messages:	Push Notifications
C:	Coaching
MR:	Meal Replacements

2. Treatment: WFS+Messages

Date of Review:

Reviewer:

Coach:

Participant ID:

Participant Week:

Condition/components:

- Is the participant recording in the APP? (Y/N) Y = 1, N=1
  - If no: MIA protocol followed? (Y/N) Y=1
- Was participant re-randomized? (Y/N) Y=0, N=1
  - Did the re-randomization occur per protocol? (Y/N) Y=1
  - Which week? (1-12)
  - Why? (Nonresponder/MIA)
  - Were the re-randomization details tracked in the "Randomization Tracking" form in the "SMART Randomization and Coaching" project? (Y/N) Y=1
- Was the participant supposed to be re-randomized? (Y/N) Congruent with prior question = 1

SCORING: */5 (if re-randomized)
*/3 (if not re-randomized)

3. Treatment: WFS+C

Date of Review:

Reviewer:

Coach:

Participant ID:

Participant Week:

Condition/components:

- Was participant re-randomized? (Y/N) Y=0, N=1
  - Did the re-randomization occur per protocol? (Y/N) Y=1
  - Which week? (1-12)
  - Why? (Nonresponder/MIA)

    - Were the re-randomization details tracked in the "Randomization Tracking" form in the "SMART Randomization and Coaching" project? (Y/N) Y=1
- Was the participant supposed to be re-randomized? (Y/N) Congruent with prior question = 1

- IN COACHING CALL:
    - Was the physical activity goal discussed? (Y/N) Y=1
    - Was the calorie goal discussed? (Y/N) Y=1
    - Was the fat gram goal discussed? (Y/N) Y=1
- To what extent were behaviors in another condition discussed or reinforced? (Not at all, A little, Somewhat, Quite a bit, A lot) Not at all = 1
    - Were the strategies mentioned by (Participant, Lifestyle coach)
    - Indicate to what extent the interventionist reframed the strategies within the context of the appropriate treatment condition (Not at all, a little, somewhat, quite a bit, completely)

SCORING: */8 (if re-randomized)
*/6 (if not re-randomized)

If coaches bring up behaviors in another condition, deduct points. If participant brings it up, and it is **not** re-framed by the coach, deduct points.

4. Treatment: WFS+C+Messages

Date of Review:

Reviewer:

Coach:

Participant ID:

Participant Week:

Condition/components:

- Was participant re-randomized? (Y/N) Y=1, N=1
  - Did the re-randomization occur per protocol? (Y/N) Y=1
  - Which week? (1-12)
  - Why? (Nonresponder/MIA)
  - Were the re-randomization details tracked in the "Randomization Tracking" form in the "SMART Randomization and Coaching" project? (Y/N) Y=1
- Was the participant supposed to be re-randomized? (Y/N) Congruent with first question = 1

- IN COACHING CALL:
  - Was the physical activity goal discussed? (Y/N) Y=1
  - Was the calorie goal discussed? (Y/N) Y=1
  - Was the fat gram goal discussed? (Y/N) Y=1
  - Did the coach ask about the text messages? (Y/N) Y=1
- To what extent were behaviors in another condition discussed or reinforced? (Not at all, A little, Somewhat, Quite a bit, A lot) Not at all = 1
  - Were the strategies mentioned by (Participant, Lifestyle coach)
  - Indicate to what extent the interventionist reframed the strategies within the context of the appropriate treatment condition (Not at all, a little, somewhat, quite a bit, completely)

SCORING: */9 (if re-randomized)
*/7 (if not re-randomized)

If coaches bring up behaviors in another condition, deduct points. If participant brings it up, and it is **not** re-framed by the coach, deduct points.

5. Treatment: WFS+C+Messages+MR

Date of Review:

Reviewer:

Coach:

Participant ID:

Participant Week:

Condition/components:

- Was participant re-randomized? (Y/N)
  - Did the re-randomization occur per protocol? (Y/N)
  - Was the participant supposed to be re-randomized? (Y/N)
  - Which week? (1-12)
  - Why? (Nonresponder/MIA)
  - Was the participant contacted to receive meal replacements? (Y/N)
  - Was the meal replacement contact and delivery/pickup recorded in the RedCap project? (Y/N)
  - Were the re-randomization details tracked in the "Randomization Tracking" form in the "SMART Randomization and Coaching" project? (Y/N)

- IN COACHING CALL:
  - Was the physical activity goal discussed? (Y/N)
  - Was the calorie goal discussed? (Y/N)
  - Was the fat gram goal discussed? (Y/N)
  - Did the coach ask about the text messages? (Y/N)
  - Did the coach ask about the meal replacements? (Y/N)
- To what extent were behaviors in another condition discussed or reinforced? (Not at all, A little, Somewhat, Quite a bit, A lot)
  - Were the strategies mentioned by (Participant, Lifestyle coach)
  - Indicate to what extent the interventionist reframed the strategies within the context of the appropriate treatment condition (Not at all, a little, somewhat, quite a bit, completely)

SCORING: */12 (if re-randomized)
*/10 (if not re-randomized)

If coaches bring up behaviors in another condition, deduct points. If participant brings it up, and it is **not** re-framed by the coach, deduct

points.