Supplementary Online Content 1

DATA AND SAFETY MONITORING BOARD PROTOCOL AND REPORT

Innovative Approaches for Diet, Exercise, and Activity
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ABSTRACT

This study was funded in response to RFA-HL-08-007 “Targeted Approaches to Weight Control for Young Adults”. The studies funded by this RFA are included in the EARLY Trial consortium, with the study in Pittsburgh titled IDEA (Innovative Approaches for Diet, Exercise, and Activity). This study will focus on development, refinement, and evaluation of a behavioral approach to weight control in young adults, with the focus of this application being on enhancing long-term weight loss. Consistent with the RFA, young adults for this study are defined as individuals 18-35 years of age.

The prevalence of obesity in young adults has been increasing, and excessive body weight has been linked to numerous chronic conditions including cardiovascular disease, diabetes, many forms of cancer, and numerous musculoskeletal problems. The focus of this study is to develop and evaluate interventions that may be appropriate for young adults to improve weight loss outcomes following a 24 month intervention. Therefore, the primary aim of this study is to examine whether an enhanced weight loss intervention (EWLI) that includes advanced technology components results in improved weight loss in young adults (18-35 years of age) compared to a standard behavioral weight control program (SBWP) over a period of 24 months. Additional aims include examination of these interventions on changes in body composition, body fat distribution, fitness, physical activity, dietary intake, and behavioral/psychosocial measures that may be predictive of behavior change. In addition, we will examine the effects of these interventions on common elements across all studies in the Early Trial. Assessments will occur at 0, 6, 12, 18, and 24 months.

This study involves the recruitment of 480 overweight and obese young adults (18-35 years of age). Subjects will participate in a 24-month behavioral weight loss program that includes a reduction in energy intake and moderate-to-vigorous intensity exercise (progressively increasing from 100 to 300 minutes per week). Subjects will be randomized to receive this intervention (SBWP) or this intervention in combination with technology enhancements (EWLI). SBWP and EWLI will receive text messaging prompts to reinforce adherence to the behavioral intervention from months 7-24 and EWLI will wear a monitor from months 7-24 that provides real-time feedback on energy expenditure and achievement of daily physical activity goals.

It is hypothesized that these technology enhancements to EWLI will significantly improve weight loss, body composition, body fat distribution, fitness, physical activity, dietary intake, and the other common outcome elements compared to SBWP.

2. SPECIFIC AIMS

Primary Aims

1. This study will examine whether an enhanced weight loss intervention (EWLI) that includes technology components results in improved weight loss in young adults (18-35 years of age) compared to a standard behavioral weight loss intervention (SBWP) over a period of 24 months. *It is hypothesized that there will be a significant improvement in weight loss following a 24-month intervention in the EWLI intervention versus the SBWP intervention.*

Secondary Aims for Physiological Outcomes

1. This study will examine whether an EWLI intervention that includes technology components results in improved reductions in body fatness compared to a standard behavioral weight loss intervention (SBWP group). *It is hypothesized that there will be a significant improved reduction in body fatness following a 24-month intervention in EWLI versus SBWP.*
2. This study will examine whether an EWLI intervention that includes technology components results in improved reductions in body fat distribution compared to a standard behavioral weight loss intervention (SBWP group). *It is hypothesized that there will be a significant greater reduction in body fat distribution following a 24-month intervention in EWLI versus SBWP.*
3. This study will examine whether an EWLI intervention that includes technology components results in improved fitness compared to a standard behavioral weight loss intervention (SBWP group). *It is hypothesized that there will be a significant improvement in fitness following a 24-month intervention in EWLI versus SBWP.*

Secondary Aims for Physical Activity and Energy Intake

1. This study will examine whether an EWLI intervention that includes technology components results in improved increases in physical activity compared to the SBWP intervention. *It is hypothesized that there will be a significant increase in physical activity following a 24-month intervention in EWLI versus SBWP.*
2. This study will examine whether an EWLI intervention that includes technology components results in improved reductions in energy intake compared to the SBWP intervention. *It is hypothesized that there will be a significant reduction in energy intake following a 24-month intervention in EWLI versus SBWP.*

Secondary Aims for Behavioral/Psychosocial Measures

1. To examine if there are differences between the interventions (EWLI vs. SBWP) for self-efficacy, outcome expectations, barriers, motivation, and other behavioral/psychosocial measures as described in the Methods Section. *It is hypothesized that a EWLI intervention will result in significant improvement in these parameters when compared to SBWP*.

3. BACKGROUND AND SIGNIFICANCE

Prevalence and Health Impact of Overweight and Obesity

Obesity is a significant health problem in the United States , and has been linked to increases in morbidity and mortality from many chronic diseases including cardiovascular disease, diabetes, cancer, etc. [1]. In addition, it has been suggested that being overweight can significantly increase health care costs [2-4], and it is estimated that in excess of $117 billion is spent annually treating obesity and obesity-related conditions account for approximately 7 percent of total health care costs in the United States [5]. Despite these findings, the number of individuals classified as overweight has dramatically increased over the past 20-30 years, and it is now estimated that in excess of 65 percent of adults in the United States are overweight (BMI $\geq$ 25 kg/m^2) with approximately 30 percent classified as obese (BMI $\geq$30 kg/m^2) [6].

There are concerns that young adults may be particularly impacted by the increasing rates of overweight and obesity. For example, NHANES data demonstrate that the prevalence of obesity (BMI $\geq$30 kg/m^2) has increased from 26.0% in the 1999-2000 survey to 28.5% in the

2003-2004 survey in 20-39 year olds [6]. Moreover, the prevalence of severe obesity (BMI≥40 kg/m^2) has increased from 4.5% to 5.4% in 20-39 year olds from the 1999-2000 survey to the 2003-2004 survey [6]. Unfortunately, sustainable long-term weight loss has been less than desirable in this age group of 18 to 35 year old individuals as supported by data from our studies as described in the Preliminary Studies Section of this application. For example, following initial weight loss, 13% of the weight lost was regained within 6 months and 34% of the weight lost was regained within 12 months. This is of even greater concern because 18.8% of individuals aged 18-35 who initiated a weight loss program actually increased body weight by 3.0±2.6 kg (3.8±3.2% increase above initial body weight) at the 18 month assessment period. This resulted in BMI increasing from 30.8±3.8 kg/m^2 to 32.0±3.9 kg/m^2 across this 18 month period of time in our studies. Data from the CARDIA study have also reported a trend for young adults to gain weight [7].

Young adults have not been the primary focus of weight loss intervention studies, which may contribute to the lack of optimal success of these individuals with current weight loss interventions. Thus, there is a need to develop more effective weight loss programs for young adults to enhance long-term weight loss and to potentially curtail excessive weight gain in this population. *This application will examine an innovative approach to obesity treatment in young adults that if effective may provide an efficacious approach to behavioral interventions promoting long-term weight loss.*

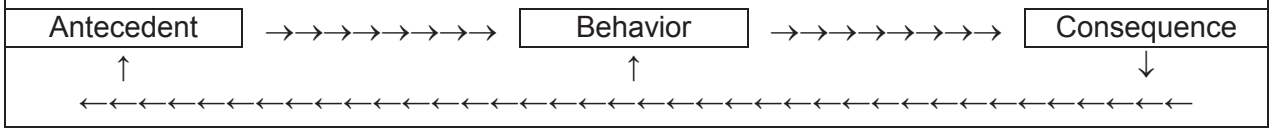
Standard Behavioral Interventions for Weight Loss

Standard behavioral weight loss programs typically involve face-to-face interventions delivered in either group or individual sessions, with these interventions focusing on a variety of behavioral strategies to enhance compliance to eating and physical activity behaviors conducive to weight loss. This form of intervention has typically resulted in weight loss of approximately 8% to 10% in the initial 6 month intervention period [8]. Data on young adults (18-35 years of age) participating in our studies show that these types of interventions are effective at reducing weight by approximately 8% to 9%. However, these data also show that weight regain was 34% of initial weight loss by 18 months (which is 1 year after the initial 6 month weight loss intervention), suggesting that long-term weight loss remains a significant challenge. *This period following initial weight loss will be the period targeted with enhanced intervention strategies of the EWLI group in an attempt to improve long-term weight loss in young adults, and this intervention is described in detail in Section D.3.c.6. below.*

Potential Theoretical Approach for Enhancing Behavioral Weight Loss Outcomes

Wing and Greeno[9] have summarized a simplified theoretical approach to modifying behaviors that will result in improved weight loss outcomes (see Figure 1). This approach focuses on strategies to impact antecedents to the desired behavior and consequences of the desired behavior. "Antecedents" are factors that precede and potentially prompt the desired behavior, whereas "consequences" follow the behavior and provide feedback on success. For weight loss, the desired behaviors are to reduce energy intake (diet) and increase energy expenditure (physical activity), and the interventions proposed for this current study will target modifications in these behaviors, with the enhanced intervention components in the EWLI group focusing on the antecedents and the consequences of the desired behaviors (eating & physical activity) to improve the desired outcome (weight loss at 24 months).

Figure 1. Simplified approach to modifying eating and physical activity behaviors for weight loss.



Based on this simplified theoretical model we propose to target antecedents (prompts to engage in targeted behaviors) and consequences (feedback on achievement of targeted behavior goals) with the additional intervention strategies within the EWLI group in this study. As outlined in the RFA there is a desire to examine technologies within interventions that target young adults. Therefore, we propose to include text messaging prompts (antecedents) to encourage young adults to engage in appropriate eating and physical activity behaviors to improve weight loss. There is evidence that use of this technology is wide-spread and is an appealing technology in young adults, especially among both Hispanic and African-Americans (PEW Internet and American Life Project report, 2008). We also propose to use technology that allows for real-time monitoring of energy expenditure and physical activity goals. This technology system provides feedback and prompts alterations in physical activity behavior and may provide information to participants that allows for adjustments in energy intake to match energy expenditure. Evidence from our laboratory shows that this technology may be an effective and appealing addition to weight loss interventions.

Summary

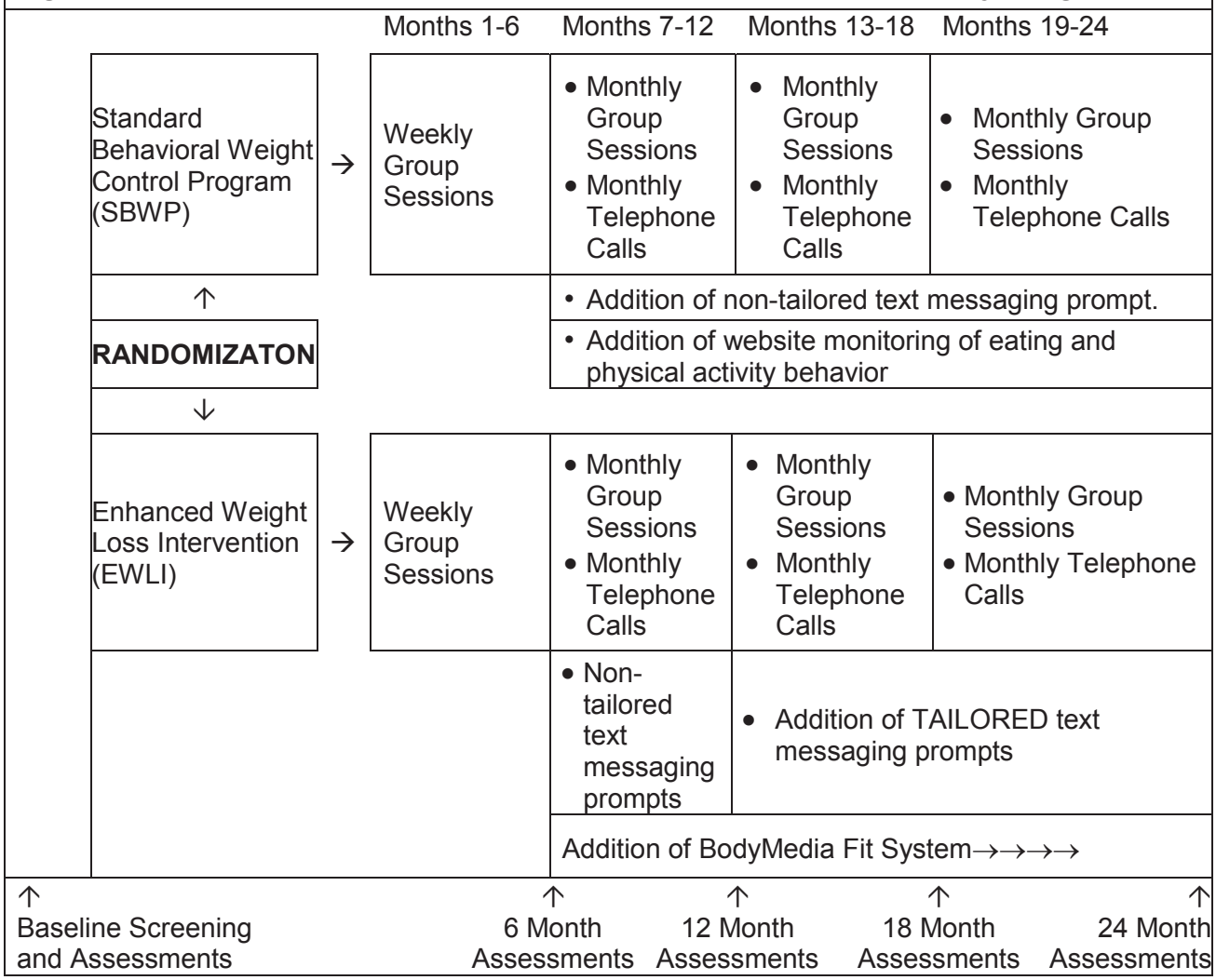
Excessive body weight that results in overweight or obesity is increasing in prevalence in the United States, especially among young adults (age 18-35 years) who appear to be affected by this concerning public health trend. Moreover, while young adults appear to respond favorably to initial weight loss efforts, the ability to sustain this weight loss long-term is less than desirable. Thus, there is a need to develop and implement intervention strategies that improve long-term weight loss outcomes. This will be the target of this 24-month weight loss intervention for young adults, with the focus on including technologies (text messaging and real-time monitoring of energy expenditure and physical activity) to improve long-term weight loss.

4. OVERVIEW OF DESIGN

This study will be a randomized clinical weight loss trial that will include modifications in both eating and exercise behaviors. Subjects will be randomized to one of the following groups (see Figure 2). In addition, outcome assessments will be performed at 0, 6, 12, 18, and 24 months.

1. Standard In-Person Behavioral Weight Control Program (SBWP): Subjects in this group will receive our standard behavioral weight control program that is delivered in an in-person group-based format. At month 7 subjects will also be given access to a study website to monitor eating and activity behaviors, and to have electronic access to standardized intervention materials. At month 7 subjects will also receive targeted study-related text messages that otherwise would have been provided in paper format.
2. Enhanced Weight Loss Intervention (EWLI): Subjects in this group will participate in a weight loss intervention that includes technology enhancements. These enhancements will include the addition of intervention specific targeted and tailored text messaging and the BodyMedia Fit System® beginning at Month 7. At month 7 subjects in EWLI will also receive the same targeted study-related text messages provided to SBWP that otherwise would have been provided in paper format.

Figure 2. Randomization, assessments, and intervention timeline and study design.



5. STUDY POPULATION AND ELIGIBILITY

We will recruit 480 overweight and obese young adults to participate in this study. We will include both men and women, with at least 50 percent being women, and genders equally divided among the intervention groups (we will make every effort to target 30% men for recruitment into this study). In addition, our sample will include a minimum of 25% minority representation. We have been able to successfully recruit this level of minority representation in prior weight loss and exercise studies that we have conducted in the Greater Pittsburgh Metropolitan area, with two current weight control interventions averaging 25-30% minority representation. *Individuals will be considered eligible if they meet all of the following inclusion and none of the exclusion criteria*:

Table 1. Inclusion and Exclusion Criteria	
Inclusion Criteria	**Exclusion Criteria**
• *18-35 years of age	• *Unable to provide informed consent
• *Intending to be available for a 24 month intervention	• *Household member on study staff
• An active cellular telephone that is capable of receiving text messaging.	• *Past or planned (within the next 24 months) weight loss surgery (e.g. gastric bypass, lap band, or liposuction); current participation in a commercial weight loss program (e.g. Weight Watcher's, Jenny Craig); current or planned enrollment in another diet/PA/weight loss intervention study.
• A computer and internet connectivity that can be used for the BodyMedia Fit system	• *Report regular use of systemic steroids, prescription weight loss drugs. “Regular use” is defined as “taking this medication most days of the week for the previous month”
• Body mass index (BMI) between 25.0-39.9 kg/m^2	• *Current treatment for eating disorder
• The ability to provide medical clearance to participate in this study from their primary care physician.	• *Cardiovascular event (heart attack, stroke, episode of heart failure, or revascularization procedure) within the last 6 months.
• The ability to complete the baseline graded exercise test, and clearance from the study physician to participate in this study after reviewing the results from this study.	• *Current treatment for malignancy (other than non-melanoma skin cancer)
	• *Currently pregnant or gave birth within the last 6 months, currently lactating or breastfeeding within the last 3 months, actively planning pregnancy within the next 24 months
	• *Investigator discretion
	• Currently taking medication that would affect heart rate or blood pressure responses to exercise (e.g., beta blockers).
	• Report losing >5% of current body weight in the previous 3 months.
	• Currently treated for psychological issues, or taking psychotropic medications within the previous 6 months.
	• Report taking medication that could affect metabolism or change body weight
	• Current treatment for diabetes mellitus
	• Reports any of the following conditions: heart disease, angina, hypertension, heart attack, stroke, cancer

*indicates Common Inclusion and Exclusion Criteria for studies within the EARLY Trial.

6. RECRUITMENT

Recruitment Sources

Subjects will be recruited using a variety of media including newspaper advertisements, television and radio advertisements, along with direct mailings and other techniques that we have used in prior studies and are approved by the Institutional Review Board at the University of Pittsburgh. We have experience working with individuals with communication and marketing backgrounds in the development of age, gender, and culturally sensitive recruitment advertisements for past research studies, and we will use similar strategies in this study.

We are currently working with the University of Pittsburgh Marketing and Communication office to develop these recruitment sources. This is involving the development of a study logo/branding, direct mail fliers, various media advertisements. Thus, our proposed recruitment approaches will include the following:

- Direct mail to communities with the age demographic
- Direct mail (paper and email) to hospital employees and university faculty, staff, and enrolled students who meet the desired demographics.
- Electronic media including the study website, craigslist, etc.
- Targeted media marketing using radio and/or television
- Other methods based on information gathered in the pilot study that is currently underway

Recruitment Process

Potential subjects will be instructed to contact the investigators via a telephone number that is provided in these advertisements. Individuals who inquire about this study will be asked to complete a brief telephone interview to assess initial eligibility, with eligible participants invited to attend a study orientation. Dr. Jakicic will provide a detailed description of the study at this orientation, and subjects will be encouraged to have all of their questions regarding their participation in this study answered.

Following the orientation, eligible subjects based on initial screening will provide written informed consent before any additional screening and/or experimental procedures are performed. Subjects will complete a physical activity readiness questionnaire (PAR-Q) and a detailed medical history prior to participating in baseline assessments, which will be reviewed by a study physician (Kavitha B. Schelbert, MD). To minimize potential risks to the subjects, all subjects will also provide written consent from their primary care physician prior to further participation in this study. We propose to recruit subjects in cohorts of approximately $\geq$40 subjects to allow sufficient randomization to each of the intervention conditions.

Recruitment Tracking

We will use similar tracking systems that we have used in prior studies. This allows us to track the number of inquiries received, the type of recruitment source (e.g., flier, radio, television, etc.) used to identify the individual, the number eligible, the number ineligible, the reason for ineligibility, and initial demographics (age, gender, race/ethnicity). Because initial screening is completed over the telephone the IRB in Pittsburgh only permits us to collect and retain limited data based on the telephone screening due to the fact that only verbal consent is obtained prior to collecting this information.

We also track the number of individuals invited to an orientation session, the number attending an orientation session, the number providing consent to participate following the orientation session, the number who complete the remaining baseline assessments, the number eligible for randomization following baseline assessments, and the number ineligible for randomization following baseline assessments and the reason for being ineligible.

Recruitment of Women and Minorities

As part of our recruitment efforts we are interested in having adequate women and minority representation. Using the above mentioned recruitment strategies we typically had ≥70 percent women representation in our prior studies, and we anticipate a similar representation in this current study. Moreover, using these strategies we have been able to recruit 25-30% minority representation in our previous studies, and we expect a similar response in this study. To assist in the recruitment of women and minorities, we will develop diverse media advertisements to target these groups, and this has been successful for previous studies. For recruitment of minority participants, the most effective strategy has been the use of targeted mailings to zip codes in our region that have a relatively high concentration of individuals identified with a minority racial/ethnic group. We will use similar strategies in this study. We will use standard NHLBI recruitment milestone reporting tables and enrollment tables to represent the gender and ethnic/racial characteristics of subjects recruited for this study. In addition, we will use common reporting tables that are proposed for the EARLY Trials.

7. DATA COLLECTION AND MEASUREMENTS

Outcomes related to the specific aims of this study, along with common assessment elements for the EARLY Trials, will be assessed. Table 2 illustrates the assessments that will be performed along with the timing of these assessments.

Table 2. Data Collection Items

Physical Measures	**0 months (Baseline)**	**6 months**	**12 months**	**18 months**	**24 months**
*#Height	X	X	X	X	X
*#Weight	X	X	X	X	X
*#Body Mass Index (BMI)	X	X	X	X	X
*Waist Girth	X	X	X	X	X
*Arm Circumference (taken from blood pressure measurement)	X	X	X	X	X
*Resting Blood Pressure	X	X	X	X	X
*Resting Heart Rate	X	X	X	X	X
***Body Composition (DXA)	X	X	X	X	X
***Fitness (graded exercise test)	X	X	X	X	X
**Blood Collection for Storage/Banking	X	X	X	X	X
**Buffy Coat Collection for Storage/Banking	X	X	X	X	X
Dietary Measures	**0 months (Baseline)**	**6 months**	**12 months**	**18 months**	**24 months**
*#Assessment of Total Dietary Intake (Pittsburgh will use both the ASA24 and the FFQ/DHQ)	X	X	X	X	X
*Sugar Sweetened Beverage Consumption	X	X	X	X	X
*Eating Away from Home	X	X	X	X	X
*Dietary Strategies for Weight Management (includes both the required and optional items)	X	X	X	X	X
*Daily Meal Patterns	X	X	X	X	X

Physical Activity Measures	**0 months (Baseline)**	**6 months**	**12 months**	**18 months**	**24 months**
*#Paffenbarger Exercise Habits Questionnaire	X	X	X	X	X
*Global Physical Activity Questionnaire	X	X	X	X	X
*Sedentary Behavior Questionnaire (weekday and weekend day)	X	X	X	X	X
***Objective assessment of physical activity (SenseWear Pro Armband)	X	X	X	X	X
Required Surveys	**0 months (Baseline)**	**6 months**	**12 months**	**18 months**	**24 months**
*Demographics	X	X	X	X	X
*Smoking	X	X	X	X	X
*Alcohol	X	X	X	X	X
*Depression	X	X	X	X	X
*Sleep	X	X	X	X	X
*Physical activity neighborhood environment	X	X	X	X	X
Additional Surveys (Pittsburgh Specific)	**0 months (Baseline)**	**6 months**	**12 months**	**18 months**	**24 months**
Weight Loss Self-Efficacy	X	X	X	X	X
Physical Activity Self-Efficacy	X	X	X	X	X
Stages of Change for Exercise	X	X	X	X	X
Stages of Change for Weight Loss	X	X	X	X	X
Exercise Outcome Expectations and Barriers	X	X	X	X	X
Dietary Modification/Weight Loss Outcome Expectations and Barriers	X	X	X	X	X
CESD (depressive symptoms)	X	X	X	X	X
Weight history	X	X	X	X	X
Body Image	X	X	X	X	X
Restrained Eating (3-factor eating inventory)	X	X	X	X	X

indicates a required element in the EARLY Trials.
****indicates an optional element in the EARLY Trials.****
*****indicates an element at the Pittsburgh site.*****

#indicates measures that will also be assessed at 30 and 36 months for subjects who agree to extend their participation by 12 months (through 36 months).

A. Body Height

A calibrated stadiometer (wall-mounted or free-standing) graduated in centimeters with a horizontal measuring block (or fixed angle) will be used. The subject is to remove shoes for the measurement of height. The subject stands erect on the platform/floor with his/her back parallel to the vertical mounted measure scale, looking straight ahead with his/her head in the Frankfort horizontal plane (the horizontal plane is defined by the lower margin of the bony orbit - the bony socket containing the eye - and the most forward point in the supratragal notch -the notch just

above the anterior cartilaginous projections of the external ear). The subject should be instructed to stand as straight as possible with feet flat on the floor. The horizontal measuring block is brought down snugly, but not tightly, on the top of the head. The subject's height is recorded to the nearest 0.1 cm. The subject is asked to step away, raise measuring block and ask subject to return and repeat measure. The average of 2 measurements that differ by $\leq$0.5 cm is used to represent the height. If these criteria are not met a third measurement is to be taken. *All 3 measures are to be entered into the database, and the average of the 3 measures are to be used for study-wide analyses.*

B. Body Weight

A calibrated digital scale that measures weight to 0.1 kg will be used to assess body weight. The Pittsburgh site will maintain records of calibration, with calibration procedures including following manufacturer recommendations and the use of known weights. Calibration procedures will be performed weekly.

Ideally, body weight will measured in the morning after voiding and before breakfast. If this is not possible, efforts should be made to weigh each subject under conditions as similar as possible on all visits (e.g., same time of day, fasting, limited consumption of fluids). All measurements will be made with the participants wearing a light cloth surgical gown without shoes.

The subject should be instructed to stand still in the middle of the scale platform with the head erect and eyes looking straight ahead. Staff will record the weight in kilograms to the nearest 0.1 kg as indicated on the digital display. Ask the subject to step off the scale and check that the digital display returns to zero. The average of 2 measurements that differ by $\leq$0.2 kg is used to represent the weight. If these criteria are not met a third measurement is to be taken. *All 3 measures are to be entered into the database, and the average of the 3 measures are to be used for study-wide analyses.*

C. Body Mass Index (BMI)

BMI will be computed based on measurement of weight and height and represented as kg/m^2. Procedures for measurement of height and weight are described above.

D. Waist Girth

A Gulick Tape Measure will be used for obtaining waist girth measurements. Ideally, waist circumference would be measured in the morning after voiding and before breakfast. If this is not possible, efforts should be made to measure each subject under conditions as similar as possible on all visits (e.g., same time of day, fasting, limited consumption of fluids). Waist circumference measurements are to be made with the participants wearing a light cloth surgical gown without shoes. Measurement of waist girth will follow the procedures described in the NHANES III protocol.

- To define the level at which waist circumference is measured, a bony landmark is first located and marked. The subject stands and the examiner, positioned at the right of the subject, palpates the upper hip bone to locate the right iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal mark is drawn, then crossed with a vertical mark on the midaxillary line.
- The measuring tape is placed in a horizontal plane around the abdomen at the level of this marked point on the right side of the trunk. The plane of the tape is parallel to the floor.
- The measurement should be taken at the end of a normal exhalation, with the measurement recorded to the nearest 0.1 cm.
- The average of 2 measurements that differ by $\leq$1.0 cm is used to represent the waist

girth. If these criteria are not met a third measurement is to be taken. *All 3 measures are to be entered into the database, and the average of the 3 measures are to be used for study-wide analyses.*

E. Resting Seated Blood Pressure

A Dinamap automated blood pressure system will be used to assess resting blood pressure at the Pittsburgh site. Every attempt should be made to maintain the same equipment throughout the study period to reduce inter-equipment variability, and service records will be maintained. Cuff size will be determined by arm circumference. Each of the following cuff sizes will be available: Adult, Large Adult, Thigh and Long Large Adult. A Gulick Tape Measure will be used for measurement of the participant's arm circumference.

Seated blood pressure measurements will be done at the beginning of an assessment visit after the participant has been sitting quietly in an isolate room for at least five minutes. During this five minute resting period, participants will not be engaging in any of the following: reading, filling out forms, talking or crossing their legs or ankles.

- Selecting the appropriate cuff size: To select the appropriate cuff size it is necessary to determine the participant's right arm circumference.
  1. The right arm is to be bare with no clothing covering the arm.
  2. The participant is to hold the arm at the side of the body with the elbow flexed to 90 degrees (handshake position).
  2. On the lateral aspect of the arm measure the length of the arm from the acromion process (bony extremity that forms the highest point of the shoulder) to the olecranon process (tip of the elbow) and determine the midpoint of this length. Mark this midpoint on the lateral surface of the arm using a cosmetic pencil.
  3. With the arm relaxed and the elbow extended and hanging just away from the side of the trunk and the palm facing the thigh, place the tape measure around the arm at the midpoint mark. The tape measure is to be parallel to the floor.
  4. The average of 2 measurements that differ by ≤1.0 cm is used to represent the arm circumference. If these criteria are not met a third measurement is to be taken. *All 3 measures are to be entered into the database, and the average of the 3 measures are to be used for study-wide analyses.*
  5. Using the arm circumference measurement, determine the cuff size according to the chart that follows:

Arm Circumference	**Cuff Size**
17.0 to <24.0 cm	Small Adult
24.0 to <33.0 cm	Adult
33.0 to <41.0 cm	Large Adult
≥41.0 cm	Thigh or Large Adult Long (If a participant's upper arm circumference would indicate use of the thigh cuff, but the arm is too short for the cuff, or the cuff does not remain secured when inflated, the Large Adult Long arm cuff should be used.)

- Taking the seated blood pressure: The subject will be seated with both feet flat on the floor and the right forearm resting on the table. Staff will palpate the antecubital fossa and position the cuff around the arm so that the midpoint of the bladder length is at heart level, and the cuff arrow marked "artery" is aligned with the brachial artery. Cuffs are labeled with range and index lines. The correct cuff has been selected if the index line is within the range as the cuff is wrapped around the arm. The cuff will be wrapped snugly

enough that no more than one finger-width distance exists between cuff and skin. The participant will rest for five minutes prior to taking the first measurement. After a minimum of a 30-second wait, obtain a second measurement. Duplicate measurements with systolic blood pressure differing by ≤10 mmHg and diastolic blood pressure differing by ≤6 mmHg should be obtained. If these criteria are not met a third measurement is to be taken. *All 3 measures are to be entered into the database, and the average of the 3 measures are to be used for study-wide analyses.*

F. Resting Seated Heart Rate

The Dinamap automated blood pressure system also provides a measure of heart rate. Thus, resting heart rate will be measured simultaneously with the measures of resting blood pressure as described above. The heart rates which correspond to the resting blood pressure measurements that are used for data analysis will be used to determine the average resting heart rate.

G. Body Composition

Body composition will be assessed using a GE Lunar iDXA dual-energy x-ray absorptiometer (Lunar, Inc., Madison, WI). This technique will provide a measure of fat mass, lean body mass, bone mineral content, bone mineral density, and percent body fat. Subjects will be clothed in a lightweight hospital gown and will be instructed to remove all jewelry, hairpins, etc. that would potentially affect the accuracy of this measurement. In addition, to ensure that none of the subjects are pregnant, all female subjects will complete a urine pregnancy test immediately prior to their DXA assessment. Women who are pregnant will be excluded from this study. The scanner will be calibrated each day according to the guidelines specified by the manufacturer.

H. Fitness

Subjects will participate in an assessment of cardiorespiratory fitness. Subjects will be requested to abstain from vigorous activity for 24 hours prior to the assessment period. Subjects will be placed in a seated position for a period of 10 minutes, and this will be followed by assessment of resting blood pressure, and resting heart rate using the R-R technique described by Dubin [10]. ACSM criteria will be used to exclude subjects from this study for whom exercise is contraindicated [11] based on the results of this exercise test.

The protocol that Dr. Jakicic in developing for the multi-center Look AHEAD Study will be adopted for this study [12]. The speed of the treadmill will be kept constant at 3.0 mph (80.4 m/min) with the initial grade of the treadmill being 0% and increasing at 1.0% increments at 1-minute intervals. Heart rate during exercise testing will be obtained at one-minute intervals using a 12-lead ECG (Marquette Instruments) and immediately upon termination of the exercise test. Blood pressure will be obtained during each even minute (2 min, 4, min, 6 min etc.) and immediately upon termination of the exercise test. Rating of perceived exertion [13] will be assessed during the final 15 seconds of each minute and at the point of test termination. The test performed to assess cardiorespiratory fitness will be a submaximal test. This submaximal test will be terminated at the time when the participant first achieves or exceeds 85% of age-predicted maximal heart rate (HR_{Max} = 220 minus age). A physician will evaluate the results of each exercise test to ensure that exercise training is not contraindicated.

Oxygen consumption will be measured continuously using a SensorMedics Vmax Spectrum metabolic cart, with gas volumes and concentrations calibrated according to manufacturer specifications prior to each test. Fitness will be expressed in absolute (L/min) and relative terms (ml/kg/min and ml/kgLBM/min). Change in cardiorespiratory fitness will be computed as the difference between these values on the baseline test and on the subsequent tests. NOTE: We have selected a submaximal test to assess fitness in this study as these tests

have been shown to be sensitive to change in fitness in populations similar to the subjects being recruited for this proposed study [14, 15].

I. Blood Collection and Buffy Coat Collection for Storage/Banking

- Fasting Requirements: Participants are required to fast for a period of 12 hours prior to the blood draw. This is to be documented and confirmed with the subject.
- Sample Collection: Several tubes of plasma, serum, and a sample for DNA material will be collected and retained in long-term storage. Specifically the following samples will be collected and stored in 2 ml cryovials (with a threaded cap) in a -70º freezer (range: -75º to -65ºC). All participants will have 25 mls of blood drawn for the core exam, using the following vacutainers:
    - One 10-ml lavender top (EDTA) vacutainer tube (can be used for analysis of lipids and other similar assays, and also used for collection of buffy coat);
    - One 10-ml red top (SST) vacutainer tube (can be used for analysis of insulin, glucose, creatinine and other similar assays);
    - One 5.0-ml blue top (citrated) vacutainer tube (can be used for analysis of C-reactive protein, IL-6, fibrinogen, and other similar assays).
- Procedures: We proposed to adapt the procedures from the CARDIA Study for standardized collection of blood samples for use in the EARLY Trial studies. (See: http://www.cardia.dopm.uab.edu/pdf/mooy20/Y20%20Phlebotomy.pdf.)
- Labeling of Stored Samples: We propose to adopt a standard method of labeling across sites within the EARLY Trial studies. This will involve bar coding of samples using standard methodology.
- Storage of Samples:
    - Samples are to initially be stored at individual sites in 1.8 - 2.0 ml cryovials with a threaded cap with an "O" ring (i.e., Sarstedt 1.8 ml cryovial) in a -70º freezer (range: -75º to -65ºC).
    - Buffy coat at each collection visit is to be stored separately in cryovial vials from the 10-ml lavender top (EDTA) vacutainer tube.
    - Documentation of integrity of storage will be maintained.
        - The *Daily Temperature Record* will be completed each day the clinic is in operation. Freezer, refrigerator and room temperatures are to be recorded.
        - The acceptable temperatures are:
            - freezer: -75º to -65ºC;
            - refrigerator: 35º to 40ºF;
            - room: 65º to 75ºF.

J. Dietary Measures

The Pittsburgh site will use two dietary measures that are recommended as common measures for the EARLY Trials, which will allow for post-hoc comparisons between these measures of dietary intake.

1. **ASA24**: The ASA24 is a software tool that enables automated and self-administered 24-hour dietary recalls. The format and design **of** ASA24 **are** based on a modified version of the interviewer-administered Automated Multiple Pass Method 24-hour recall developed by the U.S. Department of Agriculture (USDA). AMPM uses multi-level food probes to accurately assess food types and amounts. The ASA24 will be used at each assessment period to assess dietary intake on two separate days.
2. **Diet History Questionnaire (DHQ)**: The DHQ is a food frequency questionnaire (FFQ) developed by staff at the Risk Factor Monitoring and Methods Branch of the

National Cancer Institute. This FFQ consists of 124 food items and includes both portion size and dietary supplement questions. The DHQ will be completed at each assessment period.

3. Additional Common Dietary Measures Developed for the studies involved in the EARLY Trials
    a. Eating Away from Home
    b. Dietary Strategies for Weight Management
    c. Daily Meal Patterns

K. Physical Activity Measures

1. Paffenbarger Exercise Habits Questionnaire: The questionnaire developed for the Harvard Alumni Study to assess leisure-time physical activity will be adapted for this study.

2. Global Physical Activity Questionnaire (GPAQ): The GPAQ that was developed by the World Health Organization will be adapted for this study.

3. Sedentary Behavior Questionnaire: The sedentary behavior questionnaire developed for CARDIA will be adapted for this study.

4. Objective Assessment of Physical Activity: For the objective measure, we propose to use the *SenseWear Pro Armband®*. This will involve subjects wearing the armband for 7 consecutive days at the intervention assessment periods (0, 6, 12, 18 and 24 months) to provide an objective measure of physical activity. Data from the armband are downloaded to a computer using an interface provided by the manufacturer to allow for further analysis of these data using software developed through the Physical Activity and Weight Management Research Center at the University of Pittsburgh.

L. EARLY Trials Required Surveys

The following required surveys for the EARLY Trials will be used in this study.

- Demographics
- Smoking
- Alcohol
- Depression
- Sleep
- Physical activity neighborhood environment

M. Additional Surveys: Pittsburgh Site Specific

- Self-Efficacy for Weight Loss and Physical Activity: Self-efficacy is one of the central constructs in social cognitive theory. Self-efficacy for weight loss will be assessed using the questionnaire developed by Clark et al. [16] Self-efficacy for exercise will be assessed using the questionnaire by Marcus et al. [17]. The internal consistency of the 5-item self-efficacy measure is 0.76, and the test-retest reliability is 0.90 when assessed over a 2-week period.
- Stages of Motivational Readiness for Change: The instrument developed by Marcus et al. [17, 18] will be used to assess the stages of behavior change for exercise. The Kappa index of reliability for the stages of change over a 2-week period is 0.78, with concurrent validity demonstrated by the significant association with the 7-day Physical Activity Recall questionnaire. We will use the questionnaire developed by Simkin-Silverman et al. [19] to assess stages of change for weight loss.
- Outcome Expectations: The questionnaire developed by Steinhardt and Dishman [20] will be used to assess outcome expectations for physical activity. Internal consistency coefficients for this measure range from .47 to .78, with test-retest stability correlations ranging from .66 to .89. We have used this measure in previous weight loss and exercise studies.

Participants will also report their expectation for weight loss (how much weight loss they want to achieve). This is a single question item that we have used in prior weight loss research studies. We propose to modify this questionnaire to make it specific to eating behavior and weight loss.

- Perceived Barriers: The questionnaire developed by Steinhardt and Dishman [20] will be used to assess perceived barriers for physical activity. Internal consistency coefficients for this measure range from .47 to .78, with test-retest stability correlations ranging from .66 to .89. We propose to modify this questionnaire to make it specific to eating behavior and weight loss.
- Depression: The Centers for Epidemiological Studies Depression Scale (CES-D) will be used to assess changes in depressive symptoms.
- Body Image: The Multidimensional Body-Self Relations Questionnaire (MBSRQ) will be used to assess body image [21](13).
- Dietary Restraint (3-factor eating inventory): Thes three-factor eating questionnaire developed by Stunkard et al. [22] will be used to assess changes in dietary restrain, disinhibition, and hunger.

8. QUALITY ASSURANCE AND QUALITY CONTROL

Intervention: Standardized training will be provided for all intervention staff prior to the implementation of this intervention. This training will rely on the expertise and experience of the investigators and will be modeled after successful lifestyle interventions. For example, Drs. Jakicic and Otto have trained interventionists and have conducted quality control for the multi-center Look AHEAD [12, 23] and Dr. Otto was also involved in these procedures for the Diabetes Prevention Program [24] and the CALERIE Study. Information will be presented with both didactic and interactive methods. During the intervention there will be weekly meetings to discuss issues related to the implementation of the intervention.

Assessments: Standardized training will be provided for all assessment staff prior to the implementation of this study. This training will rely on the expertise and experience of the investigators and will be modeled after successful studies conducted under their supervision. Quality control will involve retraining prior to each assessment period, and inter-assessor reliability checked on 5 random subjects during each assessment period. During the study there will be regular meetings of the investigators to monitor this aspect of the study and to take corrective action when necessary.

Data Entry and Data Quality: Descriptive and exploratory data techniques are a critical first stage of the analytic process, aiding in data quality control. The Epidemiology Data Center (EDC) has extensive experience in data management to maximize data quality assurance and control. Data are subjected to extensive edit checks for completeness, accuracy, and consistency. Reports are provided to the clinical center personnel for error resolution, updates are applied as they are received, and the updated data are subject to the same comprehensive set of edit checks. Clean data are exported from the central database and imported directly into SAS.

Human Subjects: All of the investigators on this project have completed the mandatory education in Human Subjects Research that is required by the local institutions. At minimum, the training includes reviewing educational material in Research Integrity, Human Subjects, and HIPPA.

9. RANDOMIZING AND MASKING

Randomization

For this study a total of N = 480 subjects (240 per intervention) will be randomized to EWLI and SBWP interventions using a stratified block randomization with variable block sizes, where race and sex will be used as strata. The randomization will be conducted by a web-based system, with a manual backup system. Participants will be allocated to an intervention arm within strata defined by race and sex. The web-based system will be located in a private and secure area of the server to be used for the study. The web-based system will query the user for the information required to identify the stratum (racial group X sex) and other information to enable checks that the correct subject was assigned (e.g., subject ID) and return the next intervention assignment in that stratum to the user.

Masking

Similar to the process that we have used in other multi-center clinical trials (i.e., Look AHEAD), assessment staff will be masked to intervention randomization. Thus, staff assigned to assess the outcomes of this study will not have access to randomization information and will not be present when on-site intervention sessions are being conducted. Moreover, intervention staff will not assist with data collection or data entry resulting from assessment visits. We have the capacity to limit access to electronic and paper files to retain the masking of staff, and we will implement those procedures in this study.

The investigators (Dr. Jakicic, Dr. Otto, Dr. Helsel, Dr. Marcus) will be masked to outcome data summarized by treatment arm. However, the biostatistical investigators (Dr. Belle, Wahed, King) will not be blinded to outcome data summarized by treatment arm and will prepare those components of the DSMB reports.

10. INTERVENTIONS

Overview of the Interventions

This study will be a randomized clinical weight loss trial that will include modifications in both eating and exercise behaviors. Subjects will be randomized to one of the following groups (also see Figure 1 above).

1. Standard In-Person Behavioral Weight Control Program (SBWP): Subjects in this group will receive our standard behavioral weight control program that is delivered in an in-person group-based format. At month 7 subjects will also be given access to a study website to monitor eating and activity behaviors, and to have electronic access to standardized intervention materials. At month 7 subjects will also receive targeted study-related text messages that otherwise would have been provided in paper format.
2. Enhanced Weight Loss Intervention (EWLI): Subjects in this group will participate in a weight loss intervention that includes technology enhancements. These enhancements will include the addition of intervention specific targeted and tailored text messaging and the BodyMedia Fit System® beginning at Month 7. At month 7 subjects in EWLI will also receive the same targeted study-related text messages provided to SBWP that otherwise would have been provided in paper format.

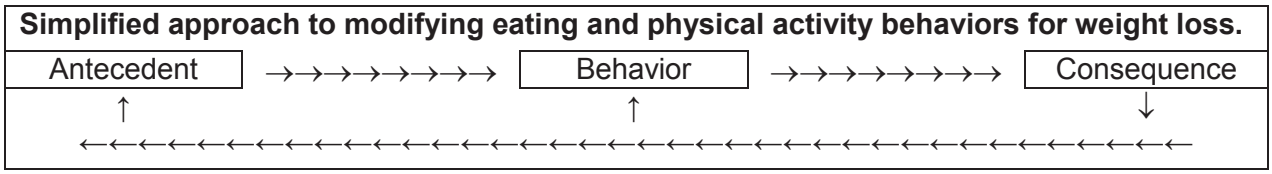
The specific details of each of the intervention groups are described in detail below.

Theoretical Rationale/Model Underlying the Interventions

Standard behavioral weight loss programs typically involve face-to-face interventions delivered in either group or individual sessions, with these interventions focusing on a variety of behavioral strategies to enhance compliance to eating and physical activity behaviors conducive to weight loss. This form of intervention has typically resulted in weight loss of approximately 8% to 10% in the initial 6 month intervention period [8]. Data on young adults (18-35 years of

age) participating in our studies show that these types of interventions are effective at reducing weight by approximately 8-9%. However, these data also show that weight regain was 34% of initial weight loss by 18 months (which is 1 year after the initial 6 month weight loss intervention), suggesting that long-term weight loss remains a significant challenge. *This period following initial weight loss will be the period targeted with enhanced intervention strategies of the EWLI group in an attempt to improve long-term weight loss in young adults.*

Wing and Greeno[9] have summarized a simplified theoretical approach to modifying behaviors that will result in improved weight loss outcomes (see Figure below). This approach focuses on strategies to impact antecedents to the desired behavior and consequences of the desired behavior. "Antecedents" are factors that precede and potentially prompt the desired behavior, whereas "consequences" follow the behavior and provide feedback on success. For weight loss, the desired behaviors are to reduce energy intake (diet) and increase energy expenditure (physical activity), and the interventions proposed for this current study will target modifications in these behaviors, with the enhanced intervention components in the EWLI group focusing on the antecedents and the consequences of the desired behaviors (eating & physical activity) to improve the desired outcome (weight loss at 24 months).



Based on this simplified theoretical model we propose to target antecedents (prompts to engage in targeted behaviors) and consequences (feedback on achievement of targeted behavior goals) with the additional intervention strategies within the EWLI group in this study. As outlined in the RFA there is a desire to examine technologies within interventions that target young adults. Therefore, we propose to include text messaging prompts (antecedents) to encourage young adults to engage in appropriate eating and physical activity behaviors to improve weight loss. There is evidence that use of this technology is wide-spread and is an appealing technology in young adults, especially among both Hispanic and African-Americans (PEW Internet and American Life Project report, 2008). We also propose to use technology that allows for real-time monitoring of energy expenditure and physical activity goals. This technology system provides feedback and prompts alterations in physical activity behavior and may provide information to participants that allows for adjustments in energy intake to match energy expenditure. Evidence from our laboratory shows that this technology may be an effective and appealing addition to weight loss interventions.

Description of Interventions

Standard In-Person Behavioral Weight Control Program (SBWP)

Intervention Contact: Subjects in this intervention group will receive our standard behavioral weight control program that is delivered in a group format consisting of approximately 20 participants. To minimize contamination, these will be closed group meetings that are limited to participants randomly assigned to the SBWP group. Group sessions typically last 55-60 minutes, which permits time to distribute intervention materials, interact with each participant, identify participants that need additional support, and conduct the group intervention.

Intervention contact will be based on our experience in conducting weight loss and physical activity interventions that have been 12-24 months in duration. Through these experiences we have determined that maintaining a high frequency of contact with subjects is important for maintaining recommended physical activity and eating behaviors, and this is consistent with the chronic-care model for long-term weight control proposed by Perri and

colleagues[25]. During the initial 6 months of treatment, participants will attend weekly in-person group intervention sessions. During months 6-24, participants will attend one group session per month and one brief (≤10 minutes in duration) telephone contact per month. (NOTE: for subjects who agree to extend their participation by 12 months the telephone contacts will occur every other month between months 25-36.) The group session will allow for social support from other group members, while the telephone calls will allow for tailored individual contact with each participant. This is similar to the protocol that we previously used and are currently using in our standard behavioral weight loss interventions. To facilitate transportation to these sessions and to enhance retention over the period of 24 months, free parking is provided and an extensive mass transit system is available to participants.

Beginning with Month 7 subjects in SBWP will receive standardized text messaging prompts to remind them of study visit or intervention telephone calls that have been scheduled, and this will replace "paper" reminders that are typically sent to subjects as part of our standard behavioral interventions.

Behavioral Lesson Content: Each group visit will focus on a specific behavioral topic related to weight loss, eating behaviors, or exercise behaviors. Discussion related to this topic will be facilitated by the interventionist, and interactive group participation will be encouraged. An example list of the topics that are typically included in in-person group sessions is provided in Appendix C, and participants are provided written materials to supplement the group discussion. Attempts are made to schedule make-up sessions when an individual misses an in-person session, and in the event that this is not possible, participants are mailed all intervention materials and are to review them prior to the next group meeting. Beginning with Month 7 subjects in SBWP will be given access to a study website that will allow them to access standardized intervention materials electronically rather than in a paper format.

Self-Monitoring: Self-monitoring is an important component of behavioral weight loss interventions. Participants will monitor body weight, eating behaviors, and exercise behaviors. Body weight will be measured at each in-person group meeting and participants will also be encouraged to measure their body weight on their own during weeks when no in-person visits are scheduled (e.g., months 7-24).

Participants will be encouraged to self-monitor their eating and exercise behaviors throughout the intervention period. Participants will be provided with a weekly diary to record eating and exercise patterns. Participants will return the completed diary to the intervention staff at each in-person visit for review, and the intervention staff will provide written feedback on the diary prior to it being returned to the participant. The diaries will also be used to generate discussion with the participant during the weigh-in period and within the in-person group session. Participants will also be provided with self-addressed stamped envelopes to facilitate the return of these diaries in the event that they need to miss an in-person visit.

- (Note: Participants identified as engaging in eating and exercise behaviors that are deemed to be unsafe will be contacted and receive appropriate counseling from the investigators.)
- (Note: Diaries are used as an intervention tool and are not providing data for statistical analysis.)

Beginning with Month 7 subjects in SBWP will be given access to a website that provides them the ability to self-monitor their eating and activity behaviors on this website rather than using the paper diary.

Dietary Recommendations: All subjects will be prescribed an energy restricted dietary intervention that we have shown to effectively reduce body weight by 8-10% within the initial 6 months of treatment. This will include reducing energy intake to 1200 to 1800 kcal/d based on initial body weight (<200 pounds = 1200 kcal/d; 200 to 250 pounds = 1500 kcal/d; >250 pounds = 1800 kcal/d). Data from our research studies [14, 15] and the National Weight Control Registry [26] indicated that macronutrient composition in the most successful participants

consists of 20-30% dietary fat intake, 50-55% carbohydrate intake, and 20-25% protein intake. Therefore, a similar dietary composition will be recommended in this study. However, we do recognize that low carbohydrate/high protein diets are currently popular, have demonstrated some initial efficacy, and some participants may gravitate towards this macronutrient composition, and this will be acceptable provided that total energy intake is within the prescribed range. To facilitate the adoption of the dietary recommendations, individuals will be provided with meal plans (see Appendix B), that will allow them to plan for modifications in their daily and weekly meal plans, and a calorie counter book.

Exercise Recommendations: Participants will be prescribed exercise that is consistent with data that have shown that higher levels of exercise may be important for preventing weight regain [14, 15, 26-29]. Specifically, subjects will be instructed to engage in moderate intensity exercise 5 days per week. The total duration per day will begin at 20 minutes per day and will gradually progress to at least 60 minutes per day, as this level of exercise has been shown to be associated with improved long-term weight loss [14, 15, 26-29] and is recommended by leading organizations [27, 30-32]. Exercise will be progressed in a gradual manner (5-10 min/d in 4 week intervals) in an attempt to maximize adherence and minimize the onset of musculoskeletal injury. This is similar to our typical exercise progression, and we have found that this progression results in minimal injuries that limit exercise participation. We have previously demonstrated that permitting overweight participants to accumulate their exercise in multiple 10-minute exercise sessions per day enhances the initial adoption of exercise [33, 34]. Thus, this will be an option for participants in this study. Exercise intensity will be set at 55-70% of age-predicted maximal heart rate, which corresponds to 11-13 on the 15-category Rating of Perceived Exertion (RPE) Scale. Jakicic et al.[14] reported that when prescribed this intensity, overweight/obese adults exercised at a heart rate of approximately 115-126 beats per minute and at a RPE of 12, and we anticipate similar compliance in this proposed study.

Enhanced Weight Loss Intervention (EWLI)

Intervention Contact: Intervention contact in EWLI will be the same as the contact described above for SBWP and will include a combination of both in-person and telephone-based intervention contact.

Behavioral Lesson Content: The behavioral lesson content will be the same as the behavioral lesson content described above for SBWP.

Self-Monitoring: Standard self-monitoring techniques using a weekly diary will be the same in EWLI as that described above for SBWP.

Dietary and Exercise Recommendations: The dietary and exercise recommendations are identical to those prescribed for SBWP.

In addition, EWLI will receive intervention enhancements to prompt individuals using text messaging to sustain recommended changes in eating and physical activity (beginning at Month 7), and to provide immediate real-time feedback on physical activity and energy expenditure using the BodyMedia Fit System (beginning at Month 7). These enhancements are described in detail below.

Text Messaging: We have developed an automated text messaging system to prompt individuals to enhance recommended behavior change strategies consistent with the behavioral content of the intervention sessions. Through our pilot testing we have found this system to be compatible with all existing cellular telephone systems (e.g., AT&T, Sprint, Verizon, etc.) available to individuals in our demographic area.

Text messaging prompts **in both** SBWP and EWLI will begin at Month 7 and continue through Month 24 of this study. A pilot study is currently underway to determine the optimal number (1, 2, or 3 per day), optimal time of day to receive these messages, and nature of the content of these messages. Based on this formative work that is underway, the text messaging system will be modified prior to implementation in the intervention phase of this study.

We considered providing cellular telephones with text messaging capabilities for all subjects randomized to EWLI. However, our pilot data showed that in excess of 95% of individuals who expressed interest in participating in a recent weight loss intervention reported having a cellular telephone with text messaging capabilities. Therefore, we propose only to recruit individuals with a cellular telephone with text messaging capabilities to participate in this study, rather than incur the expense of providing a cellular telephone to all participants. We do recognize, however, that there is a cost incurred by individuals for text messaging ranging from $5-$10 per month depending on the cellular provider. Therefore, we will reimburse individuals in EWLI $10 per month to offset the text messaging costs so that this does not become a financial burden for individuals assigned to EWLI.

Immediate Real-Time Feedback on Physical Activity and Energy Expenditure: As described above, individuals in EWLI will be provided with a BodyMedia Fit System that includes a Minifly® armband and a real-time display of minutes of moderate (≥3 METS) and vigorous (≥6 METS) intensity physical activity and total daily energy expenditure. Use of the BodyMedia Fit System in EWLI will begin at Month 7 and continue through Month 24 of this study. (NOTE: for subjects who agree to extend their participation by 12 months the BodyMedia System will be extended for use between months 25-36.) Individuals will be instructed to wear the armband during all waking hours on their upper left arm midway between the shoulder and elbow over the triceps muscle as described by the manufacturer. Individuals will be instructed to remove the armband prior to going to sleep for the evening and to recharge the unit with the charger that is provided which plugs into a standard electrical outlet.

Participants will be taught how use the information provided by the BodyMedia Fit System to alter their physical activity behaviors to achieve the intervention goals and to adjust their energy intake based to facilitate weight loss and prevention of weight regain based on their total energy expenditure provide by this system. Examples of how this information will be used to alter behavior are provided below:

1. Adjustment of physical activity behaviors: The physical activity goal of this study is to increase to at least 60 minutes of moderate-intensity physical activity on at least 5 days per week (300 min/wk). The BodyMedia Fit System will provide real-time feedback on achievement of this physical activity goal. Thus, subjects in EWLI will be able to determine at any moment during the day whether they have achieved this goal, and they will be taught strategies for increasing activity throughout the day to achieve this activity goal based on the real-time feedback they receive from this technology.

2. Adjustment of energy intake based on daily energy expenditure: The BodyMedia Fit system also provides real-time feedback on total daily energy expenditure. This information can be helpful to participants when adjusting their daily energy intake to facilitate weight loss and/or weight loss maintenance. Thus, subjects in EWLI will be taught strategies for altering their energy intake throughout the day based on the real-time feedback received from this technology.

Standardizing Delivery of the Intervention

Standardized training will be provided for all intervention staff prior to the implementation of this intervention. This training will rely on the expertise and experience of the investigators and will be modeled after successful lifestyle interventions. For example, Drs. Jakicic and Otto have trained interventionists and have conducted quality control for the multi-center Look AHEAD [12, 23] and Dr. Otto was also involved in these procedures for the Diabetes Prevention Program [24] and the CALERIE Study. Information will be presented with both didactic and interactive methods. During the intervention there will be weekly meetings to discuss issues related to the implementation of the intervention.

Facilitating Participants' Retention in the Intervention

We have been able to successfully maintain 80% to 90% of subjects in studies that are at least 18-24 months in duration, and the retention rates have been similar across ethnic groups. Our most recent 24-month study resulted in retention rates of 90% in White/Caucasian, 87.5% in African-American/Black, and 100% in Hispanic/Latino. We propose the following strategies for retention.

1. Subjects will provide contact information including address, home telephone number, work telephone number, and email address.
2. As commonly used in clinical trials, subjects will complete a "Participant Contact" form that will include the name, address, telephone number, and email address of at least two family members or close friends who will know the location of the participant throughout the intervention.
3. Subjects will be mailed birthday cards, holiday cards, and program reminders, and when undeliverable they are returned with a forwarding address.
4. We will use behavioral contracts at multiple time points during recruitment, assessment, and after randomization to support our retention efforts and to determine the understanding of subjects regarding the requirements for study participation. This strategy appears to have enhanced adherence rates to the intervention and assessment schedules in prior studies.
5. We will use a study website that will allow subjects to view their calendar of events scheduled assessment and intervention sessions. In addition, this will allow us to automate reminder emails to the subjects. Dr. Jakicic and colleagues at the University of Pittsburgh have developed a web-based system to serve this purpose for ongoing research projects at the University of Pittsburgh, which will be adapted to this proposed study. An eligibility requirement is that subjects have access to a computer and the internet.
6. We propose staff training to provide consistency in content delivery and will also focus on relationship building between the intervention team and the subjects. Dr. Jakicic has used this strategy successfully when retaining 96% of randomized subjects across a 6 month intervention with 92% of subjects being retained following 12 months of the intervention [14], and 89% of subjects being retained following 24 months of the intervention [15].
7. There will be mandatory weekly clinical meetings involving the PI and the intervention team related to the intervention protocol, problem-solving issues that arise, and retention of study participants. This will be modeled after the clinical intervention team meetings and retention strategies that have been used in the multi-center Look AHEAD Study and other ongoing intervention studies conducted by Dr. Jakicic and colleagues at the University of Pittsburgh.

11. SAFETY MONITORING

Potential Risks

Table 3. Potential risks of study participation.		
Assessment Activity	**Common Risks**	**Infrequent Risks**
Risks associated with DXA to assess body composition	The DXA involves exposure to radiation which is about 0.05 mrem per total body scan.	
Risk Associated with the Completion of Questionnaires	The subject may experience non-physical risks such as boredom, frustration, stress, and time constraints when completing the questionnaires	
Risks of Exercise Testing		
• Risk of breathing in and out of a metabolic cart	The subject may experience a dry mouth.	
• Risk of Electrocardiogram (ECG)	The subject may experience skin irritation or redness from electrodes being placed on the skin.	
• Risks of Exercise Testing	The participant may experience an increase in heart rate, an increase in blood pressure, shortness of breath, general fatigue, and in some cases muscle soreness	During exercise the individual may experience a serious cardiac event, an arrhythmia. The possibility of experiencing a serious cardiac event has been estimated to be approximately 6 per 10,000 in exercising adults.
Risks of Wearing the SenseWear Pro Armband	Some people may experience mild skin irritation where the armband is worn. Specifically, the build-up of sweat that can be trapped between the skin and the armband, or not properly cleaning the armband, can cause pink pustules or pimples to appear. This condition is named miliaria, or prickly heat.	
Intervention Activity	**Common Risks**	**Infrequent Risks**
Risk of Exercise Participation	Exercise may cause an increase in heart rate, an increase in blood pressure, shortness of breath, general fatigue, and in some cases muscle soreness or injury to the muscle, bone, or joint.	Exercise may cause the subject to experience a serious cardiac event, an arrhythmia, or chest pain. The possibility of experiencing a serious cardiac event has been estimated to be approximately 6 per 10,000 in exercising adults.
Risks Associated with Participating in Group Intervention	Attendance at group intervention sessions may involve subjects sharing information about themselves and their weight loss efforts to other group members. The investigators cannot guarantee that all group members will keep this information confidential, there is risk that group members may share information about the group session with individuals not participating in this study.	

Risks of Reducing Calorie and Fat Intake	If the subject reduces calorie and/or fat intake below recommended levels they may experience dry skin or thinning of their hair.	Reduced calorie and/or fat intake may also result in gall bladder problems that includes intense abdominal pain, nausea, or vomiting. Other symptoms may include bloating, gas, or indigestion
Risks of Wearing the BodyMedia Fit Armband	Some people may experience mild skin irritation where the armband is worn. Specifically, the build-up of sweat that can be trapped between the skin and the armband, or not properly cleaning the armband, can cause pink pustules or pimples to appear. This condition is named miliaria, or prickly heat.	

Expected Adverse Events

Over the two-year duration of the study a number of medical events may be expected to occur, including malnutrition, bone loss, gall bladder disease, musculoskeletal problems, motor vehicle accidents, diabetes, hypertension, dyslipidemia, liver disease. Expected events that occur as a result of a protocol violation are treated in the same way as unexpected events and will therefore require expedited reporting to the NHLBI.

Serious adverse events are defined as the occurrence of any acute life-threatening event, a hospitalization for any cause other than routine delivery, prolonged or permanent disability, pregnancy resulting in a congenital abnormality or birth defect, a major cardiovascular event, or cancer other than non-melanoma skin cancer.

Evidence of the occurrence of adverse events is based on participant self-report that a health care professional has diagnosed the condition, and no attempt is made to verify the diagnosis. Participants are also monitored at every data collection visit through the 24-month visit for the occurrence of heart trouble; stroke, TIA, or other neurological problems; new diagnosis or hospitalization for diabetes; new diagnosis, started treatment or hospitalized for depression or any other mental health problem; eating disorders; pregnancy; or muscle or bone injury. All other outcomes that may be construed as being an adverse consequence of study participation, such as an injury while performing a study measurement, are documented, reviewed, and followed up by a study clinician as needed.

Surveillance and Reporting Procedures

Reports submitted to the DSMB will cover participant recruitment, intervention session attendance rates, retention rates, AE and SAE summaries and classifications, data quality control, response to previous DSMB recommendations, and any additional information requested by the DSMB. Separate systems will be put in place to handle the report of AE's and SAE's to the DSMB and the IRB at the University of Pittsburgh in a timely fashion after adjudication. *These procedures are being standardized across the EARLY Trials.*

In addition to the data review by the DSMB, all data (not intervention data based on group assignment) will be reviewed monthly. This will include review of participant recruitment procedures and the recruitment timeline. Data that will be monitored to assess completion of the proposed assessments at each of the assessment periods, documentation of any adverse events that may occur, initial review of medical history and PAR-Q, and review of study data to insure that outcome data are within acceptable criteria.

Data will also be reviewed to assess whether there is any change in the risk-to-benefit ratio of this study. If potential safety concerns are identified that change the benefit-to-risk ratio,

the DSMB will be alerted along with the local IRB to determine the proper course of action to address these safety concerns.

Procedures will be reviewed to ensure that data are being collected in a manner to protect the confidentiality of subjects. All subject information will be coded with a study identification number to maintain confidentiality. In addition, all study data will be locked in a secured area (e.g., locked file cabinet).

The Investigators will submit the following data to the local IRB at the time of each annual renewal. However, this information may be submitted more frequently when necessary to ensure the safety of subjects in this study.

a. The frequency of monitoring that took place during the renewal interval.
b. A summary of the cumulative adverse event data including a respective assessment of experimental intervention causality.
c. A summary of the assessment that was performed to evaluate external factors or relevant information that may have an impact on the safety of study participants or ethics of the research study.
d. A summary of the outcome of procedural reviews conducted to ensure subject privacy and research data confidentiality.
e. Final conclusions regarding changes to the anticipated benefit-to-risk ratio of study participants and final recommendations related to continuing, changing, or terminating the study.
f. If potential safety concerns are identified that change the benefit-to-risk ratio, the DSMB and local IRB will be notified to determine the appropriate course of action to address these safety concerns. All adverse events will be reported to the local IRB in compliance with the local IRB policy.

Safety Monitoring Plan

A Data and Safety Monitoring Boards (DSMB) will be appointed by the NHLBI to oversee the studies funded under this mechanism. The investigators on this application are willing to participate in the DSMB meetings as outlined in the RFA, and we have appropriately budgeted to attend these meetings along with all steering committee meetings. We are willing to conform to all policies and procedures outlined by the DSMB and will work with the DSMB to integrate these into existing policies and procedures as required by the IRB at the University of Pittsburgh.

The investigators on this project will also meet regularly to review and implement the data and safety monitoring plan (DSMP) at the University of Pittsburgh (described above). This review group will consist of at least Dr. Jakicic (PI), Dr. Belle (Biostatistician), Dr. Brat-Schlebert (Physician), and Dr. Otto (Intervention).

Safety Alerts

Safety alert values for all participants undergoing baseline assessment and all subjects randomized to participate in the intervention are show below in Table 4.

Table 4. Alert values for all participants undergoing baseline assessment and all subjects randomized to participate in the intervention.

MEASUREMENT	ALERT VALUE	ACTION TO BE TAKEN
RESTING BLOOD PRESSURE	Systolic blood pressure ≥180 or Diastolic Blood Pressure ≥110 mmHg	If at baseline, advise participant to see provider within 1 week. Give advice within 24 hours of measurement If during the intervention consult with study physician to suspend or modify intervention and advise participant to see provider within 1 week. Give advice within 24 hours of measurement.
	Systolic Blood Pressure 160-179 or Diastolic Blood Pressure 100-109 mmHg	Advise participant to see provider within 1 month. Give advice within 1 week of measurement. If during the intervention consult with study physician to suspend or modify intervention and advise participant to see provider within 1 week. Give advice within 24 hours of measurement.
	Systolic Blood Pressure 140-159 or Diastolic Blood Pressure 90-99 mmHg	Advise participant to see provider within 3 months. Give advice within 1 month of measurement. If during the intervention consult with study physician to suspend or modify intervention and advise participant to see provider within 1 week. Give advice within 24 hours of measurement.
	Systolic Blood Pressure <90 mmHg	At study visit, ask participant about dizziness; if yes, advise participant to see provider within 1 month. Give advice at study visit. If during the intervention consult with study physician to suspend or modify intervention and advise participant to see provider within 1 week. Give advice at study visit when measurement occurred.
LABORATORY TESTS *Safety action only required if lab results are available within 6 months	LDL > 160 mg/dl	Advise participant to see provider within 3 months. Give advice within 1 month of the time the study staff receives the lab result
	Triglycerides >= 500 mg/dl	Advise participant to see provider within 3 months. Give advice within 1 month of the time the study staff receives the lab result
	Blood sugar <60 mg/dl	Advise participant to see provider within 3 months Give advice within 1 month of the time the study staff receives the lab result
	Blood sugar > 126 mg/dl	Advise participant to see provider within 3 months Give advice within 1 month of the time the study staff receives the lab result
GRADED EXERCISE TEST		
Heart rate/Rhythm	Abnormal heart rate rhythm as identified by study physician that would contraindicate exercise and/or weight loss.	Advise the participant at the study visit or within 24 hours of receiving notification from the study physician. Advise the participant to see provider or other medical personnel within the timeline recommendation by the study physician. If during the intervention consult with study physician to suspend or modify intervention. Advise the participant to see provider or other medical personnel within the timeline recommendation by the study physician.

MEASUREMENT	ALERT VALUE	ACTION TO BE TAKEN
Blood Pressure	Blood pressure response that occurs during the graded exercise test that would contraindicate exercise and/or weight loss as determined by the study physician.	Advise the participant at the study visit or within 24 hours of receiving notification from the study physician. Advise the participant to see provider or other medical personnel within the timeline recommendation by the study physician. If during the intervention consult with study physician to suspend or modify intervention. Advise the participant to see provider or other medical personnel within the timeline recommendation by the study physician.
DEPRESSIVE SYMPTOMS	≥13 score on the 10-item CES-D	The study staff will calculate the CES-D score within 2 weeks of data collection and to have the Principal Investigator or study clinician/safety officer review and confirm any values of 13 or higher. For those with a score of 13 or higher, a letter from the study will go out to the respondent within 2-4 weeks of their data collection telling them of their score, and referring them to their personal physician or other appropriate healthcare provider. This letter will also included resources that the participant may find helpful when seeking care along with emergency information should these symptoms worsen.
INAPPROPRIATE WEIGHT LOSS BEHAVIORS	The participant responds with an answer of "1 or higher" to any of the following questions: 1. How many times per week on average over the past 3 months have you made yourself vomit to prevent weight gain or counteract the effect of eating? 2. How many times per week on average over the past 3 months have you used laxatives or diuretics to prevent weight gain or counteract the effects of eating? 3. How many times per week on average over the past 3 months have you fasted (skipped at least 2 meals in a row) to prevent weight gain or counteract the effects of eating?	The participant is to complete the EDDS (Eating Disorder Diagnostic Scale) Questionnaire. [Stice et al. Psychological Assessment. 2000, 12(2):123-131]. Standard published criteria for bulimia nervosa from the EDDS will be used to identify participants who meet the criteria for bulimia nervosa [Stice et al. Psychological Assessment. 2000, 12(2):123-131]. These criteria include the following: a. regular eating binges marked by a perceived loss of control and the consumption of a large amount of food as indexed by a response of *yes* to EDDS Item 5, a *yes* to EDDS Item 6, and a response of greater than 2 on EDDS Item 8; and b. regular use of compensatory behaviors as indexed by a response of 8 or greater on the sum of EDDS Items 15, 16, 17, and 18; and c. undue influence of body weight or shape on self-evaluation as indexed by a score of 4 or greater on either EDDS Item 3 or 4. The following procedures will be used if the participant meets the criteria for bulimia nervosa based on the EDDS: a. If the criteria are met for bulimia nervosa at baseline, the participant will be excluded and referred to an appropriate mental health professional for additional screening and/or treatment. b. If the criteria are met for bulimia nervosa at any follow-up period (6, 12, 18, 24, 30, or 36 months), the participant will be removed from the study intervention and referred to an appropriate mental health professional for additional screening and/or treatment.

MEASUREMENT	ALERT VALUE	ACTION TO BE TAKEN
WEIGHT	Rapid weight loss (>6%/month)	Advise participant to see provider within 1 month. Give advice within 1 month. If during the intervention consult with study physician to suspend or modify intervention (specific procedures for intervention modification are provided below**). Advise the participant to see provider or other medical personnel within the timeline recommendation by the study physician.
	BMI < 18.5 kg/m^2	Advise participant to see provider within 1 month. Give advice within 1 month. If during the intervention consult with study physician to suspend or modify intervention (specific procedures for intervention modification are provided below**). Advise the participant to see provider or other medical personnel within the timeline recommendation by the study physician.

<u>Intervention Modification for Weight Loss that Exceeds 6% per Month</u>**

Within the IDEA Study, if a participant exceeds 6% per month the subject will be advised of the following as per the EARLY Trials protocol:

1. Advise participant to see provider within 1 month. Give advice within 1 month.
    a. Adjustments to the intervention may be made based on the findings of the primary care physician. These adjustments will be made in consultation with the study physician.
2. If during the intervention, consult with study physician to suspend or modify intervention. Advise the participant to see provider or other medical personnel within the timeline recommendation by the study physician.

The modifications to the intervention will include the following:

1. As part of the intervention the subject is instructed to self-monitor dietary intake and return weekly self-monitoring diaries to the intervention staff for review. Thus, in the case of weight loss >6% per month, the intervention staff will that includes registered dietitians will closely examine these self-monitoring diaries and make appropriate dietary recommendations to slow weight loss that may include
    a. Increasing the daily and weekly energy intake goals and recommending specific modifications to food choices. This will be done in consultation with the study physician.
    b. In situations where the dietary intake appears to be appropriate based on self-monitoring, the intervention staff will recommend strategies to the participant to confirm the accuracy of self-monitoring of dietary intake.
    c. In situations where self-monitoring is not occurring regularly, the intervention staff will recommend strategies to improve the frequency of self-monitoring to allow the attainment of dietary intake information that may inform the intervention staff of the cause of this rapid weight loss.
2. As part of the intervention the subject is instructed to self-monitor physical activity and return weekly self-monitoring diaries to the intervention staff for review. Thus, in the case of weight loss >6% per month, the intervention staff that includes exercise physiologists will closely examine these self-monitoring diaries and make appropriate physical activity recommendations to slow weight loss that may include
    a. In the case where physical activity is at or below the targeted weekly level, the exercise physiologist will work in collaboration with the registered dietitians to adjust the daily and weekly energy intake goals to more appropriately match the acceptable weight loss goal. This will be done in consultation with the study physician.
    b. In the case where physical activity is above the targeted weekly level, the exercise physiologist will counsel the participant to adjust the physical activity level to match the recommended levels for this study.

c. In situations where both physical activity and dietary intake appear to be appropriate based on self-monitoring, the intervention staff will recommend strategies to the participant to confirm the accuracy of self-monitoring of these behaviors.
d. In situations where self-monitoring is not occurring regularly, the intervention staff will recommend strategies to improve the frequency of self-monitoring to allow the attainment of information that may inform the intervention staff of the cause of this rapid weight loss.

****Intervention Modification for Reduction in Body Mass Index (BMI) to <18.5 kg/m^2**

Within the IDEA Study, a goal weight loss is established with the participant. This includes a minimum target of 10% of initial body weight, and this target is not to exceed a level that will reduce BMI below 22 kg/m^2. At the point when a participant achieves a BMI of $\leq$22 kg/m^2 the following will occur:

1. The energy intake goal (daily and weekly) will be adjusted to allow for weight maintenance. This will be based on estimates of total daily energy expenditure that includes an estimate of resting energy expenditure and energy expenditure from physical activity. If weight stability does not occur within 2 weeks the energy intake goal will be further adjusted until weight maintenance is achieved.

If weight loss results in the BMI reducing to <18.5 kg/m^2 the following will occur:

1. According to the EARLY Trials protocol, the participants will be advices to see their provider within 1 month, and this advice will be given within 1 month of the study staff becoming aware of this situation, or in a shorter time period if recommended by the study physician.
2. Consultation with the study physician will occur to suspend or modify intervention. Modification to the intervention may involve the following:
    a. The energy intake goal (daily and weekly) will be adjusted to allow for weight to increase so that BMI is $\geq$18.5 kg/m^2. This will be based on estimates of total daily energy expenditure that includes an estimate of resting energy expenditure and energy expenditure from physical activity. If this does not occur within 2 weeks, the energy intake goal will be further adjusted until BMI is $\geq$18.5 kg/m^2.
    b. In the case where physical activity is above the targeted weekly level, the exercise physiologist will counsel the participant to adjust the physical activity level to match the recommended levels for this study. The level of physical activity may also be adjusted downward along with a concurrent increase in energy intake to facilitate achievement of a BMI $\geq$18.5 kg/m^2.

12. POWER AND SAMPLE SIZE

We calculated the sample size based on the paired t-test [35]. Based on our pilot studies, the mean (sd) weight losses (in lbs) from baseline were 15.3 (11.4), 13.3 (14.2) and 10.1 (14.8) respectively at months 6, 12, and 18. If a similar trend of weight change continues until month 24 among SBWP group, expected weight loss would be about 7.5 lbs at 24 month. We hypothesize that the EWLI group will have 5 lbs more weight loss, the EWLI group needs to lose at least 12.5 lbs by the end of month 24. Using a standard deviation of 15 lbs for both groups, a two-sided t-test at 5% level of significance will have 90% power to detect a mean difference of 5 lbs (effect size of .33) between EWLI and SWBP group if 24 months data were available for at least 191 patients in each group. From our previous experience we expect that there will be an attrition of 20%. Adjusting for the attrition rate of 20%, 238 patients need to be recruited in each group to achieve such power.

13. ANALYSIS PLAN

Descriptive and exploratory data techniques are a critical first stage of the analytic process, aiding in data quality control, illuminating data patterns, and guiding further modeling. For both collected and created outcome and explanatory variables, we will examine univariate distributions using graphical methods and descriptive statistics. Bivariate relationships will also be examined graphically and utilizing statistics e.g., measuring association. The distribution of baseline characteristics between EWLI and SBWP groups will be compared using Wilcoxon's test or t-test (as appropriate) for continuous variables and using chi-square or Fisher's exact test (as appropriate) for categorical variables. Graphical descriptive techniques (e.g., spaghetti plots) will be used to describe weight losses over time. Here are the analyses plans for specific aims:

Analysis Plan for the Primary Specific Aim: Primary aim of this study is to examine whether an enhanced weight loss intervention (EWLI) that includes technology components results in improved weight loss in young adults (18-35 years of age) compared to a standard behavioral weight loss intervention (SBWP), with change in body weight from baseline to 24 months being the primary outcome. Although, the power of this study was calculated based on t-test (for simplicity), since data are collected over time (at months 0, 6, 12, 18, and 24), one needs to account for the correlation between the repeated measures taken from the same individuals while comparing two weight losses between EWLI and SBWP groups over time. Furthermore, since the subjects will be recruited in cohorts, the analysis will need to account for the correlation between two subjects belonging to the same cohort. Linear mixed model is the appropriate statistical technique for conducting such analysis when the response variable (weight) is normally distributed and the weight change over time is linear [35, 36]. Factors that would be investigated are the intervention (EWLI vs. SBWP), time (continuous), cohort and time and intervention interactions. Since the randomization will be stratified by race and sex, the model will adjust for the stratification by race, by having race and sex as a factors in the model. In addition, time and cohort will also be treated as random factors to account for the correlation between repeated measures from the same subject and the correlation between subjects belonging to the same cohort. We will treat time as discrete variable, allowing for a comparison between baseline and other time points.

The primary hypothesis will be tested by fitting a linear mixed model with weight over time as outcome, race, sex, time, intervention (EWLI vs. SBWP) and intervention by time interaction as fixed effects, and subjects and cohorts as random effects. The model will be fitted using the likelihood methods. We will start with the following general linear model:

Weight = $(\beta^0 + b^0_i) + \beta^I$ EWLI + b^C cohort + β^R Race + β^S Sex + β^{T6} Time_6 + β^{T12} Time_12 + β^{T18} Time_18 + β^{T24} Time_24 +b^{IC} Intervention*cohort + β^{IT6} EWLI*Time_6 + β^{IT12} EWLI*Time_12 + β^{IT18} EWLI*Time_18 + β^{IT24} EWLI*Time_24 + Race and Time interaction + Sex and Time interaction

where the coefficients denoted by Greek letters (β's) are fixed parameters and b's are random coefficients normally distributed with mean zero and constant variance, and the subscript 'i' is used to indicate that the random effect is subject-specific. The subscripted time variable Time_x is the indicator for the observation at time x. In the above model, race and sex will be dichotomized following randomization scheme. Model building will proceed as follows: First we will fit the above model and test the interaction by time and race, and by time and sex using likelihood ratio test. If they are not significant at 5% level, they will be dropped from the model; otherwise they will be kept in the model. The primary test of hypothesis will be the likelihood ratio test of the H_0: $\beta^{IT24} = 0$ in the final model, which will be rejected when the Likelihood Ratio Chi-square for this parameter β^{IT24} produces a p-value less than 0.05. Rejection of this

hypothesis would indicate that the change in weight by week 24 significantly differs by intervention groups.

Note that the above model also provides opportunity for comparison of weight changes at other intermediate time points. Although, not part of primary hypothesis, we will also test the linearity of the relationship between time and weight change in the following manner, to see whether a single rate of decline can be used to characterize he weight change over time. This would be accomplished by fitting a model under the null hypothesis of linearity and then comparing the likelihoods through a chi-square test.

The weights are expected to follow a normal distribution. In the case of deviation from normality, generalized estimating equations (GEE) will be used to assess the effect of intervention over time, which does not require the distribution of weight to be normal [37, 38]. Other baseline and time-varying patient characteristics will be used as covariates in the mixed model or GEE to explore their relationship with the weight loss over time with respect to the intervention.

Analysis Plan for the Secondary Specific Aims for Physiological Outcomes

Secondary specific aims listed in A.2 aims to compare the reduction of body fatness and body fat distribution, and improvement in physical fitness between EWLI and SBWP groups. These outcomes are described in section D.4. The analysis will employ similar techniques as discussed in the analysis plan for primary specific aim by replacing the primary outcome weight with the appropriate secondary outcome. For example, the first secondary specific aim (A.2.1) of the study examines whether an EWLI intervention that includes technology components results in improved reductions in body fatness compared to SBWP group. Since body fatness is described in terms of several variables (lean body mass, bone mineral content, bone mineral density, and percent body fat), the analysis will be conducted separately for each of these outcomes. Each of these outcomes will be described using descriptive statistics and graphical techniques (box plot, spaghetti plots). Linear mixed model or GEE analysis will be conducted with body fatness as the dependent variable and intervention, time, and race as the covariates with additional random effects of time and cohort. In the cases where data is categorized (% body fat over or below a cut-off), a non-linear mixed effect model will be utilized for the analysis. Since the analysis uses multiple outcomes, an adjustment for multiple comparisons will be made (see below).

Analysis Plan for Secondary Specific Aims for Physical Activity and Energy Intake

The study will examine whether the EWLI intervention results in improved increases in physical activity compared to the SBWP intervention. Physical activity (PA) will be measured in two ways: using objective monitoring, and using PAR questionnaire. The objective monitoring data will be available as minutes above 3 METS and will be treated as a continuous variable. Therefore statistical methods described for the primary aim will be used to analyze the change in PA over time and compare the changes between the intervention groups. Similarly, from the PAR questionnaire daily energy expenditure will be calculated at a given time point (months 0, 6, 12, 18, 24). Thus, again, a linear mixed model or GEE will be appropriate to study the change in energy intake over time in relation to the intervention.

To examine whether an EWLI intervention results in improved reductions in energy intake compared to the SBWP intervention, we will use linear mixed models or GEE (as appropriate) with body fatness as the dependent variable and intervention, time, and race as the covariates with additional random effects of time and cohort.

Analysis Plan for Secondary Specific Aims for Behavioral/Psychosocial Measures

Self-efficacy, outcome expectations, barriers, motivation, and other behavioral/psychosocial measures are measured at the months 0, 6, 12, 18, and 24. Changes in these outcomes over time will be analyzed using linear or non-linear mixed models depending

on the nature of the outcome and the relationship (linear or non-linear) over time. Although most of these outcomes are continuous, for example, adherence could be dichotomized as adherent or non-adherent based on how closely the subject follows the intervention.

Multiple Comparisons

Since multiple outcomes are being compared between two intervention groups, it is necessary to adjust the significance levels to account for the fact that when multiple outcomes are compared, some outcomes may appear to be significantly different, only by chance. We will use Holm's step-down Bonferroni method to adjust the p-values [39].

Missing Data

It is the consensus within the IDEA investigators that the missing weights can be regarded as missing at random (MAR), meaning that the probability that a weight measurement at a specific time will be missing depends only on the data collected prior to that time (e.g. weight at previous visit). Since the primary analysis uses the likelihood method for inference, the inference will be unbiased under this MAR missing mechanism. Therefore, the primary analysis (and other secondary analyses using likelihood-based method) will not be affected by the presence of missing data.

However, we will conduct sensitivity analyses to the above MAR assumption by using other missing data analysis methods. Primary alternative method for sensitivity analyses will be multiple imputations. Multiple imputations use the observed data to fill in the missing values repeatedly to give rise to multiple "pseudo-complete" datasets. We will impute the missing weight data 10 times using two different methods of imputation (i) MCMC imputation, and (ii) regression imputation. For this we will use the SAS procedure Proc MI (http://support.sas.com/rnd/app/papers/miv802.pdf). Each method will give rise to 10 different imputed data sets. We will fit our final model described before to each of these imputed datasets and then compute an overall estimate of the intervention effect as an average of the imputation-specific estimates. The standard error of the overall intervention effect estimate will be calculated using Rubin's formula (40, Chapter 9). SAS procedure Proc MIANALYZE will be used to implement these tasks. Overall estimates from MCMC and Regression multiple imputation will then be compared to the likelihood-based estimate from the analysis of primary aim.

14. DATA MANAGEMENT

The Epidemiology Data Center (EDC) will be responsible for all aspects of data processing and storage. The EDC has a number of data entry and management systems currently in use on many research projects that require distributed data entry but we propose a web-based system for this study, given the volume and the type of data that will be collected. The core of the data management and communications system will be a project website, which will include public and private areas, a shared document section, and a system area. Public areas of the website will include items such as a home page with a project description and current news regarding the study, and may be used as a recruitment tool. Private areas of the website will include items such as a personnel directory, project calendar, and a shared document section. In the private area, sections with restricted access to the appropriate individuals or groups will be setup for participants, DSMB members, and for data systems.

The data system area of the website will be the interface for the data entry and data management system. The web-based system interface provides a comprehensive set of tools to perform data management processes such as data entry, data verification, data editing, data updating, and report generation. Additionally, clinical center personnel will be able to query the database and generate up-to-date reports. The proposed system will allow us to program extensive real-time data validation to verify the authenticity of participant IDs, prohibit duplicate

entries, incorporate range checks, and verify that the entry matches the expected format and data type. These, and many other features, ensure that complete and highly accurate data are transmitted promptly to the EDC. Rigorous point-of-entry checks are implemented so that data entry errors can be resolved immediately before transmitting data to the central database. More extensive edit checks are executed on the main project database. Edit reports are provided to the clinical center personnel for error resolution. Corrections to records are tracked with an electronic audit trail.

EDC personnel also have extensive experience with data received electronically from outside sources. For data submitted to the EDC using systems outside of the EDC, data management personnel contact appropriate personnel to ensure compatible formats and proper Participant IDs on each record. These personnel work together with investigators to develop quality control procedures. Data dictionaries and file layouts are discussed and agreed upon prior to data transmission. The EDC has the capability to accept data submitted via secure file transfer protocol or via upload to a secure area of the project website. The EDC currently has dedicated servers that support SSL encryption used to receive and send data in a variety of ways across several research projects. Data received from all sources are subjected to extensive edit checks for completeness, accuracy, and consistency. Reports are provided to the clinical center personnel for error resolution, updates are applied as they are received, and the updated data are subject to the same comprehensive set of edit checks. Clean data are exported from the central database and imported directly into SAS.

Security: Any data system must be governed by a well-defined and enforceable security policy. Therefore, we have a strictly enforced security policy at the EDC that includes recommended standard operating procedures specifically addressing key security risk areas. Procedures include password protection, limited access to study computers, encryption, IP restriction, basic or digest authentication, and firewalls between the Internet and the EDC network and servers. Regularly scheduled backups and archives are performed with backup media copies of project files stored off-site in a secure location. Virus detection will be enforced at the EDC. All servers will be connected to uninterruptible power supplies and housed in a raised-floor computer room with alarm.

Resource Sharing

The NIH supports the concept of data sharing. We are familiar with preparing data and documentation for archives that make the data available for public use. Dr. Belle oversaw the archiving of the original data from REACH and REACH II at the National Archive of Computerized Data on Aging (NACDA), a central data repository maintained at the University of Michigan. Ms. Lawlor worked with the NIDDK-funded data repository at the Research Triangle Institute (RTI) on the process of archiving documentation and data from the Virahep-C project for which Dr. Belle was the EDC PI. Moreover, Drs. Jakicic, Otto, and Marcus are investigators on multi-center clinical trials (e.g., Look AHEAD, HEALTHLY) and are familiar with data sharing policies and procedures for these studies. Hence, personnel proposed for this project have experience disseminating study data and supporting documentation.

Ancillary Studies: It is anticipated that there will be requests for ancillary studies to accompany the main study, not only from investigators involved in this study, but also from outside investigators. The investigators from the Pittsburgh site, which consist of Drs. Jakicic and Belle along with other co-investigators, will promote this as it is believed that there are numerous opportunities outside the funding scope of this main application. Requests for these types of access to the data will be forwarded to the Principal Investigator along with co-investigators that make-up an “Emerging Science and Ancillary Studies Committee,” and this committee will evaluate the application to determine its appropriateness for an ancillary study. To apply an investigator must submit a 5 page application that includes an introduction, background and justification, and specific aims. The application will include specific hypotheses, outcome variables, analysis plans, and mock tables to show how the study will be

presented. It will be required that a co-investigator from this main application along with one of the statisticians serve as co-investigators on any approved ancillary study. If the study is approved, they will work with the investigators of the approved ancillary studies to create a complete study protocol and help them submit for funding. This will ensure that the integrity of the main study is not compromised as well as solidify the science of the ancillary studies. We expect to be able to have the major results of the main study published within one year of locking the study database.

Additional Data Sharing: Within one year after locking of the main study database and all approved ancillary study databases, Dr. Belle and the data management team will develop an archived data system to facilitate additional data sharing requests. The dataset will be submitted to the National Heart, Lung, and Blood Institute (NHLBI) of the NIH following the policies outlined (see https://biolincc.nhlbi.nih.gov/new_data_set_policy/). Data will be prepared by the study coordinating center and sent to the NHLBI after publication of the primary clinical trial results. These data will be available for release once they are received and checked by the NHLBI. The data sets will be submitted to the NHLBI no later than 3 years after the final visit of the participants to their clinical trial sites or 2 years after the main paper of the trial has been published, whichever comes first. The documentation and data should be in a general format that is accessible to the larger scientific community and well-documented. All regulations concerning participant confidentiality (e.g., eliminating identifying information) will be followed.

15. TRIAL ORGANIZATION

Clinical trials are complex and a carefully planned organizational structure must be in place to facilitate smooth operations, adherence to the study protocol, and maintenance of quality control. We will implement an organizational structure that has many features of the multi-center trials in which the investigators have participated (Look AHEAD, DPP, LABS, etc). The following committee structure is proposed for this study.

EARLY Trials Steering Committee: Dr. Jakicic will represent the Pittsburgh site on this committee. In the case where he is unable to attend an in-person or teleconference meeting he will appoint one of the co-investigators to represent the Pittsburgh site.

IDEA Study Steering Committee: This committee will be charged with the overall governance of study conduct and will consist of Drs. Jakicic, Belle, Otto, Bhat-Schelbert, and Helsel. This committee will oversee the following sub-committees that will be formed to support this study. The Steering Committee will approve the final protocols and manuals of operations, supervise the overall execution of the trial, generate and approve study policies, consider modifications of the protocol and study operations, and plan and draft study-related publications. The Steering Committee will appoint and charge the subcommittees described below. The Steering Committee will convene monthly.

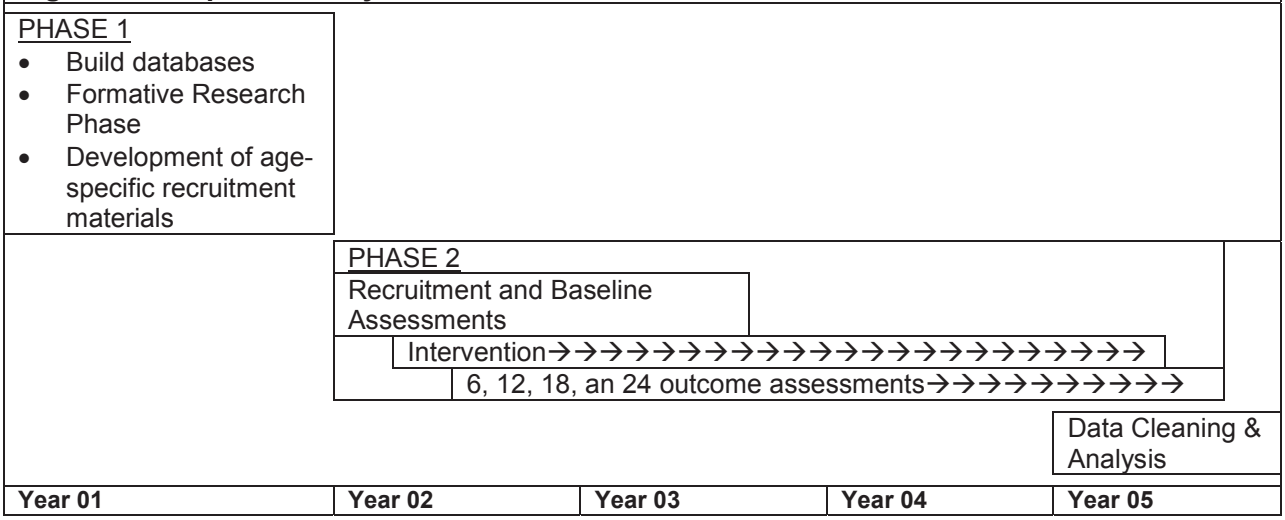
- Intervention Committee: This committee will be responsible for the development of the intervention and will also be responsible for monitoring the quality control of the intervention, training and certifying all project intervention staff involved in the intervention protocols, and assisting interventionists with problem solving and related adherence strategies throughout the course of the intervention. This team will consist of individuals with expertise in behavioral, physical activity, and nutrition.
- Recruitment, Adherence and Retention Committee: This committee will implement protocols and strategies for recruitment, adherence and retention of study participants. The Committee will help with tailoring of the recruitment messages, developing media campaigns, and developing recruitment material and forms. This committee will be responsible for developing training materials for these functions, and in monitoring performance of all Field Centers in the application of these components of the protocol.
- Publications and Presentations Committee: This committee will encourage production of high

quality publications and presentations in a timely fashion, encourage broad participation by the study investigators in publications and presentations, and assure accurate maintenance of a database on study publications. The committee will develop a detailed set of procedures for Publication and Presentation guidelines. In general these guidelines will require investigators to submit an analysis plan that describes the primary goal, data sets and variables needed, statistical methods and co-authors. After it is determined that there is no overlap with other proposals or papers, the committee will review the analysis plan and, if needed, provide comments and suggestions. Manuscripts will be reviewed and approved by at least two study investigators who are not involved as co-authors and who will be appointed by the Chair of the Publication and Presentations Committee. An electronic archive of all study publications and analysis proposals will be maintained by the Publications and Presentations Committee and will be accessible to all study investigators.

- Emerging Science and Ancillary Studies Committee: This committee will monitor the literature, scientific meetings and input received from colleagues on the cutting-edge science related to topics that are relevant to the proposed project, and will advise the Steering Committee on emerging scientific issues that may affect the conduct and future directions of the proposed study. The Committee will also review and approve plans for ancillary study proposals, including those that involve utilization of biological samples. It is very likely that additional research questions will be identified and developed.
- Measurement Committee: This committee will oversee the implementation of the assessment protocols and quality control procedures. In addition, members of this committee will be involved in quality control of measures over the course of this study, and to train new staff in the event of staff turnover during this study.

16. TIMELINE

Figure 3. Proposed study timeline.



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