Study of Novel Approaches to Weight Gain Prevention (SNAP) - Extended (SNAP-E)
Protocol
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1. EXECUTIVE SUMMARY

This project will follow the participants in the Study of Novel Approaches to Weight Gain Prevention (SNAP), a randomized clinical trial that has successfully reduced weight gain in young adults over an average of 3 years. SNAP is the first weight gain prevention trial to show positive effects over an extended time period in this age group. SNAP-E (Extension) will determine whether the effects of the intervention can be maintained over an additional 3 years (i.e. through a total of 6 years).

Young adults, ages 20-35, gain on average 2 pounds per year, increasing their risk of developing obesity and obesity related co-morbidities. Previous efforts to prevent this weight gain have had limited success. SNAP is a randomized controlled clinical trial involving 599 participants, age 18-35 with a BMI of 21-30, comparing weight changes over an average follow-up of 3 years in a control group and two interventions. Both interventions are based on a self-regulation model, involving frequent self-weighing and changes in eating and activity if weight gain occurred. However, one intervention focuses on making small consistent changes in eating and exercise behavior to prevent weight gain; the other emphasizes periodic larger changes in eating and exercise, with a goal of producing a buffer against anticipated weight gains. SNAP has had excellent retention to date and has shown that both interventions significantly reduced weight gain relative to control through 3 years. Although weight changes in the two interventions do not differ from each other at 3 years, they have had very different weight change trajectories, raising questions about long-term efficacy. Continuing to follow these participants is critical to determine whether the skills imparted during these interventions and the resulting beneficial effects on weight gain are maintained longer term and whether there are differences in outcomes for large and small change approaches.

In SNAP-E we will provide minimal intervention for the Small and Large Change groups using remote technology and will follow all participants at 6 month intervals using Smart Scales and on-line questionnaires. There will be one final clinic assessment at Year 6, with measures of body composition, cardiovascular disease (CVD) risk factors, dietary intake and objective assessment of physical activity, all implemented using procedures that were used throughout SNAP. The primary hypothesis of SNAP-E is that the magnitude of weight gain from baseline to 6 years will differ among the three arms. Secondary hypotheses compare the groups on dichotomous measures of weight gain, on CVD risk factors, and on weight control behaviors.

Preventing weight gain may be a more effective public health approach than treating obesity. SNAP is the first study to show long-term benefits of an intervention on weight gain in young adults. Continuing to follow these participants in SNAP-E provides a unique opportunity to answer important questions about longer term effects of the weight gain prevention interventions.

2. BACKGROUND

Obesity is a major health problem, affecting large numbers of adults, increasing their morbidity and mortality, and costing the US over $145 billion per year.[1] Treatment of obesity has proven difficult. Behavioral weight loss programs are successful in producing approximately 10% weight loss at one year, but over time much of this weight is subsequently regained. Physiological and behavioral factors make it difficult to reverse obesity once it occurs.[2,3] Therefore, it is critical to develop effective ways to reduce weight gain and prevent obesity.

Most efforts at prevention target children, which is clearly important. However, two-thirds of obese adults became obese during adulthood, with weight gain occurring especially between the ages of 20 and 35[4] in association with changes in lifestyle, including transitioning to a sedentary job, pregnancy, and marriage.[5,6]Data from Coronary Artery Risk Development in Young Adults (CARDIA) show that on average

young adults gain 30 pounds over this 15 year period, although more recent data suggest that the rate of weight gain may be decreasing.[7,8] Since weight gain leads to worsening in CVD risk factors,[9,10] developing effective approaches to reduce the magnitude of weight gain and prevent the development of obesity in young adults is a significant public health challenge.

The two largest and longest studies are Pound Of Prevention (POP)[11]and a study by Levine et al.[12]POP, conducted in the mid-1990s, involved approximately 1000 participants, age 20-45 with no upper BMI level, who were randomly assigned to a control group, a minimal intervention using mainly newsletters or to newsletters plus incentives. At 3 years, 63% of participants exceeded their baseline weight, with no differences between groups and mean weight gains of 1.8, 1.6, and 1.5 kg in the 3 groups respectively. In the Levine study, 284 participants, age 25-45, with a BMI <30 were assigned to a control group or to 2 years of intervention delivered either in clinic or via correspondence course. Retention was 74% at 2 years and 72% at three years. There were no significant differences in weight gain over time (+0.7, +1.3 and -0.1 kg for control, correspondence and clinic, respectively) nor in the proportion (60%) who gained >2 pounds of their baseline weight.

SNAP and SNAP-E are significant in testing two new approaches to weight gain prevention. Both interventions we are testing are based on self-regulation (see Section 7 for details). Self-regulation has been used in several prior studies, including some by this investigative team,[13,14] and been shown to be effective for both weight loss and prevention of weight regain. This is the first trial to test self-regulation interventions for weight gain prevention. In addition, SNAP and SNAP-E are testing two different approaches to weight gain prevention--one focused on making small, but consistent, daily changes in eating and exercise behavior to prevent weight gain or reverse weight gain if it occurs;[15] the other emphasizing larger periodic changes in eating and exercise, with a goal of producing small weight losses and thereby providing a buffer against anticipated future weight gains. Evidence for the small changes approach comes from theoretical papers suggesting that increases in activity of 100 kcal per day and decreases in intake of approximately 100 kcal per day should be sufficient to prevent weight gain and several empirical tests of this approach.[15-19] These small changes are expected to be easier to initiate and maintain than larger behavior changes since they represent less drastic modifications in behavior. Evidence favoring the alternative approach, of making larger periodic changes, comes from the Women's Healthy Lifestyle Project (WHLP),[20] which focused on peri-menopausal women and showed that producing initial weight losses of 5-15 pounds, even though these weight losses were followed by some weight regain, was effective in reducing the overall magnitude of weight gain and the worsening in cholesterol that occur around the time of menopause. In addition, in POP, the only individuals who remained below baseline at 3 years were those who lost weight during the initial intervention;[21]observational studies also suggest that periodic weight loss may assist with long-term maintenance.[22] Theoretically, these larger behavior changes may be easier to implement because they yield greater immediate reinforcement from the resulting weight loss and in addition, provide an opportunity for participants to practice the skills they might need to utilize if they gain weight in the future. This is the first study to compare the efficacy of a Small vs Large behavior change approach for weight gain prevention.

To date, SNAP has shown that BOTH the Large and the Small Change approaches are effective in reducing weight gain through 3 years. However, the pattern of weight change has differed dramatically in the two approaches, with greater initial weight losses, but greater regain in Large Changes. A critical question is whether either or both approaches will be more effective than the Control over a longer period of follow-up.

SNAP has also provided compelling data to show that changes in cardiovascular disease (CVD) risk factors differ significantly in those who gain 1 pound or more from baseline to 2 years compared to those who do not gain. Thus, reducing the proportion that gain greater than 1 pound, as observed in the interventions in SNAP, may have important implications for CVD risk factors in young adults.

SNAP-E builds on the success of SNAP and will continue to follow this cohort using cost-effective approaches to ongoing intervention and assessment. To date no weight gain prevention intervention for young adults has followed participants beyond 3 years. By continuing to follow participants through 6 years of follow-up, SNAP-E

will provide critical information about whether these self-regulation approaches can reduce weight gain long-term. SNAP-E will contribute to crafting a public health message for weight gain prevention by determining if the message should focus on periodic large or daily small changes.

3. Study of Novel Approaches to Prevention (SNAP)

3.1 Overview of SNAP

SNAP was a 3-armed randomized controlled clinical trial, comparing a self-regulation plus small daily behavior changes intervention, a self-regulation plus large periodic behavior changes intervention, and a minimal treatment control condition. The primary outcome was the mean of weight gain over an average follow-up of 3 years.[23] Secondary outcomes focused on weight change at 2 years and the percent remaining within 1 pound of their baseline weight at Year 2. The rationale for the trial and detailed procedures are published in BMC Public Health, 2013.[23] We recruited 599 adults (292 at the Miriam Hospital clinical site and 307 at the Univ of North Carolina site), aged 18-35 years with a BMI of 21-30 kg/m^2. Twenty seven percent were from minority groups (primarily African American) and 22% were males.[24]

3.2 Interventions in SNAP

Both intervention groups received an initial 4 month (10 sessions) face-to-face program that provided guidance in self-regulation of weight related behaviors. Self-regulation is based on a negative feedback loop in which the key components are the goal (standard of comparison), the error detector (way to determine whether the goal is being achieved), and a controlling response that is initiated if the goal is not being achieved. This model is derived from cybernetics and has been used as the foundation for a number of more recent theories about self-control[25,26] and applied in a variety of areas including diabetes[27] and obesity[13]. In SNAP, the goal was for participants to remain at their baseline weight (i.e. not gaining any weight over time). The error detector was the scale; participants in the intervention groups were taught the importance of weighing daily to detect meaningful deviations from this goal (scales were provided). To guide appropriate actions, participants were taught to use color zones to evaluate their weight, where “green” represented being at least 1 pound below baseline weight and should be followed by self-reinforcement, “yellow” is caution and problem solving is encouraged, and “red” is above baseline and requires a controlling responses to reduce the discrepancy. For both intervention conditions, the controlling responses involved changing eating and exercise behaviors to affect energy balance, but the specific recommended controlling behaviors differed by arm as shown below.

In Small Changes, the initial sessions helped them learn strategies for preventing weight gain by making daily small changes in dietary intake (about 100 kcal daily reduction) that could be consistently implemented, such as switching to low fat milk or having pizza without sausage. To increase their activity, the Small Changes group was provided with pedometers and taught ways to make small changes to increase steps by 2000 per day (about 100 calorie change) over their baseline (parking further from store; using stairs instead of elevator). Small Change participants indicated on a daily calendar if they had made a small change in eating and exercise (yes/no). They were taught that if in the future they gained weight, they should add additional small changes (e.g. make a change of 100 calories in intake at each of the 3 meals and add 2000 additional steps per day) to get back to their weight goal.

In Large Changes, the initial sessions helped them create a buffer against expected weight gain by losing 5-10 pounds (5 for normal weight/10 for overweight). Large Changes was given a weight-reducing calorie goal of 1200-1800 kcal per day (structured meal plans were provided to assist) and encouraged to gradually increase and then sustain their activity at 250 minutes per week of moderate intensity activity. They self-monitored all calories consumed and minutes of activity each day throughout the initial face-to-face program. They were encouraged to go back to self-monitoring if they later experienced weight gain and if that was not sufficient, to return to the 1200-1800 calorie diet.

After the initial face-to-face program, the interventions used primarily remote approaches to encourage frequent self-weighing and behavior change. Participants had access to a website, mobile web or texting program to submit their weights, and they were taught to use a Red, Yellow, Green system to evaluate their

own weight. They also received monthly e-mail feedback; if they were in the GREEN zone (staying below baseline weight) an e-mail was sent to reinforce their success with an occasional “green gifts’ (e.g. a dollar bill). If they were in the Yellow or Red Zone (i.e. close to or above their starting weight) they were sent an e-mail that provided helpful suggestions for re-instating the small or large changes approach. Red Zone participants were also offered additional help via email or phone. The intervention groups were also offered 2 optional 4-week annual refresher programs (conducted via on-line challenges). Again the format of the refreshers was comparable for Small versus Large Changes, but the content differed and was consistent with their original intervention.

3.3 Data Collection in SNAP

All participants were assessed at 4 months (to evaluate the initial effects of the intervention) and then annually for four years. Assessments included weight, height, bioelectrical impedance (plus BodPod at UNC only), blood pressure, CVD risk factors (at baseline and year 2), objective measures of physical activity, and questionnaires on dietary intake, weight control strategies, and psychosocial variables. Participants were recruited in 5-6 cohorts over the first 2 years of the project.

4. OVERVIEW OF TRIAL DESIGN

SNAP-E will follow the participants in Study of Novel Approaches to Weight Gain Prevention (SNAP), a randomized clinical trial that has successfully reduced weight gain in young adults through 6 years of follow-up.

Given the increasing emphasis on collection of data with cost-effective approaches[28] we will conduct SNAP-E using primarily remote technology. Participants will be followed at 6 month intervals using Smart Scales and on-line questionnaires and will conduct one final clinic assessment when the participant reaches the 6 year follow-up point. After the 6 year clinic visit, participants will be given the option to continue providing weight data using the Smart Scale. These data will address the following hypotheses:

Primary Hypothesis: The mean weight gain from baseline to 6 years will differ among the three arms. We specifically hypothesize that there will be less weight gain from baseline to 6 years in BOTH the Large and Small Change groups than in the control group. A key question is whether weight gain in Large and Small Changes will differ long-term.

Secondary Hypotheses are that the three groups will differ on the following outcomes:

1. The proportion that has transitioned to the next category (overweight or obese) and the proportion who exceed their baseline weight at year 6
2. Changes from baseline to 6 years in behaviors (diet, physical activity, frequency of self-weighing) and in use of weight control strategies
3. Changes in health outcomes, including body composition, glucose metabolism and lipid levels from baseline to 6 years

Exploratory aims are:

- Examine the associations between behavior changes, weight changes, and changes in health outcomes
- Use the data collected at 6 month intervals to compare the three groups on a) patterns of weight changes (steady rate vs alternating gains-losses), b) amount of weight gain in association with specific life events, such as pregnancy, and c) the probability of recovering from weight gains
- Using baseline characteristics and initial responses to intervention, determine characteristics of those who are “responders” to Small Changes vs Large Changes and factors that predict weight gain over time in the cohort as a whole.

4.1 Sample Size Justification

Retention in SNAP has been very high and similar among intervention groups. We assume that 450 of the SNAP participants will join SNAP-E and that going forward, attrition will accumulate at an additional 5%/year

during Years 4 to 6. To project the statistical power SNAP-E will provide for the primary outcome of weight change at Year 6, we have used the current covariance structure of the weight losses to project what this may be going forward. We generated 100,000 sequences of longitudinal data from a multivariate normal distribution with this covariance structure, randomly culled data according to the missing data assumptions above, and used this to estimate the standard error associated with the original SNAP cohort for comparing differences between intervention groups at Year 6 with a linear contrast. The standard error for this is 0.56. Using a Bonferroni adjustment for the three planned pairwise comparisons, we arrive at 80% (90%) statistical power to detect a mean difference between intervention groups of 1.81 (2.06) kg (which corresponds to about 2 years of expected weight gain in this cohort).[29]

5. STUDY POPULATION

All SNAP participants, regardless of their level of recent participation, will be asked to join SNAP-E. Participants will be invited to join via e-mail communications and a face-to-face meeting. They will sign a new consent form for SNAP-E. Those who consent to SNAP-E will be provided with a Smart Scale and a FitBit. We are projecting 450 SNAP participants will consent to SNAP-E, with similar racial/ethnic and gender make-up as observed in SNAP.

6. RETENTION

We will continue to provide ongoing intervention for the Small and Large Change groups and to follow all participants at 6 month intervals through 6 years. Follow-up data at each 6 month assessment will be collected via Smart-Scales and Internet questionnaires; the 6 year follow-up will be done at an in-person clinic visit. After the 6 year clinic visit, participants will be given the option to continue providing weight data using the Smart Scale.

We planned this approach for the following reasons. Previous studies in the area of weight control highlight the need to provide ongoing intervention to maximize long-term results.[30] The intervention we will use is low intensity and of minimal cost allowing us to continue to maintain it over long intervals, both in this research and also in future dissemination efforts. We will conduct a 6-year visit face-to-face to ensure valid measures of body weight and to collect other important outcomes, such as CVD risk factors and body composition that cannot be collected remotely. Efforts will be made to obtain these measures on all participants even if they have moved out of the area. The 6 month data will be collected via remote techniques to monitor these changes at frequent intervals with minimal cost to participants in terms of time and effort and minimal financial cost to the study. The use of 6 month assessments will provide rich data to allow us to examine the association between changes in behaviors and life events and subsequent changes in body weight. It will also allow us to maintain contact with these participants over time.

7. INTERVENTIONS

All of the components of the SNAP intervention (except the initial face-to-face sessions) will be continued in SNAP-E. This includes the following**:**

1. Both intervention groups will be encouraged to continue to weigh themselves daily. They will be provided with a Smart-Scale that transmits their weight automatically to the study, facilitating this behavior and likely further increasing engagement. They will be instructed to continue to compare their current weight to their weight at baseline of SNAP (which has been their goal weight throughout) and to take appropriate behavioral actions if a discrepancy is noted.
2. Both intervention groups will be encouraged to use FitBit devices to monitor physical activity. The Large Changes group will focus on minutes of moderate-vigorous activity whereas Small Changes will focus on steps.
3. E-mails will be sent by study staff at monthly intervals. If participants are in the Green zone (below starting weight) the e-mail will congratulate them on their success, and periodically a small “green gift” will be sent. If they are in the Yellow zone, they will be encouraged to problem solve. If they are in the Red zone, they will be encouraged to institute behaviors that are consistent with their intervention assignment: Large Changes (go back to recording your intake for 1 week; focus on getting 50 minutes

of activity on 5 days this week) or Small Changes (make small dietary change at every meal this week; increase your pedometer steps by an additional 2000 steps per day). If no weights are submitted, the e-mail will focus on the importance of self-weighing**.**

4. Twice during each year, participants will be invited to join a 4 week refresher campaign that is delivered remotely. We have had great success with these campaigns during SNAP as they have helped to re-engage participants, especially with regard to self-weighing, boosting self-weighing by approximately 10% at the start of each refresher. We are using on-line refreshers, rather than face-to-face approaches, based on our prior experiences in SNAP when refreshers 3 to 6 were delivered remotely and yielded far better engagement than earlier campaigns. During the refreshers, participants will be given a weekly behavioral challenge that focuses either on Small or Large change strategy, and they will report their weight and their success at meeting the challenge. For example, in a recent month-long refresher program 30 challenges were prescribed. For Large Changes these included "record all your intake today" or "do 45 minutes of aerobic activity today." For Small Changes, challenges included "use no sugar sweetened beverages today" and "use stairs instead of elevators/escalators today."

8. DATA COLLECTION

8.1 Assessments

We will follow participants at 6 month intervals in SNAP-E. This increased frequency of contact (over the annual visits in SNAP) is based on the ease of completing these assessments and the desire to maintain contact with this highly mobile population and capture fluctuations in weight over time. Participants will receive an e-mail informing them that it is time for their assessment, which will include weighing themselves on the Smart-Scale and completing on-line questionnaires; they will be given a $50 honorarium for completing each 6 month assessment. The year 6 assessments will be done in person and if all measures are completed, participants will receive $150 honorarium for completing this visit.

8.2 Outcome measures

Outcome measures are displayed in Table 1.

Table 1. SNAP-E Data Collection Measures

	Year			
Measure	**4 ½**	**5**	**5 ½**	**6**
Anthropomorphic				
Weight– In Clinic				X
Weight– SmartScale	X	X	X	
Height				X
Waist Circumference				X
Body Composition with Impedance				X
Body Composition with BodPod (UNC Only)				X
Behavioral				
Diet (Food Frequency Questionnaire)				X
Dietary Behavior	X	X	X	X
Physical Activity: Paffenbarger		X		X
Sedentary Activity		X		X
Objective (Accelerometer)				X
Weight Management Strategies	X	X	X	X
Self-weighing	X	X	X	X
Eating Disorders Assessment				X
Eating Inventory				X
Smoking				X
Alcohol use	X	X	X	X
Sleep habits				X
Neighborhood, Environment				X
Medical				
Blood Pressure				X
Fasting Glucose, Lipids, Insulin				X
Medication Use				X
Medical Events		X		X
Serum, Plasma				X
Psychological Assessments				
Depression (CES-D)				X
Life Events	X	X	X	X
Perceived Stress	X	X	X	X
Quality of Life	X	X	X	X
Other Questionnaires				
Demographic Data	X	X	X	X
Contact Information	X	X	X	X
Treatment satisfaction				X
Adherence (Intervention Groups only)				
Attendance at Adherence Sessions	Throughout			
Weekly Submission of Weight Data	Throughout			

8.2.1 Weight Data

The primary outcome is change in body weight at Year 6. This measure of weight will be collected at the clinic (see below) on a calibrated scale. In addition, we will collect weight data at 6 month intervals using a cellular-connected scale. In-clinic weight will be calculated as done in SNAP. Two measures will be completed and the average of the two will be used. If the difference between the two measures exceeds 0.2 kg, a third measure will be taken.

Participants will be given a Smart-Scale (BodyTrace) that transmits weight data via the cellular network; thus it does not require any connection to a computer or mobile phone. Participants will be prompted every 6 months to step on the cellular connected scale within the week and to complete on-line questionnaires at the same time. They will be instructed to weigh themselves, first thing in the morning wearing light clothing, socks and without shoes as done throughout SNAP. Three measures will be taken and averaged.

8.2.2 Clinic Visit (year 6 only)

All participants will be invited to attend one clinic visit at 6 year follow-up (6 years after randomization). An important purpose of this visit is to obtain a clinic weight so that the primary outcome of the trial is collected objectively, using procedures identical to those used for baseline weight. In addition, since weight cycling has been shown in some studies to be associated with adverse effects on body composition, [31]continuing to follow this parameter is critical. Finally, although we have not observed differences between groups in CVD risk factors thus far in the trial, previous studies show gradual worsening over time;[9] thus it will be important to determine whether there are longer term effects of the intervention on these parameters. In Look AHEAD, we found that initial weight loss, even if followed by weight regain, was associated with long term improvements in risk factors relative to never having lost weight.[32] Whether this is true in young adults has never been examined.

At this visit we will follow the assessment protocols used in prior years of SNAP[23] and in Look AHEAD.[33]Participants will attend the visit after a 12 hour fast and having refrained from strenuous physical activity for 24 hours. We recognize that some participants will have moved out of the area. We will try to arrange the visit at a time that they will be back in the area (e.g. to visit family). If that is not possible, we will collect the weight via SmartScale or through a physician's office, as a last resort, complete the questionnaires online and arrange a brief phone call to administer staff administered forms such as the Paffenbarger, CES-D and Medical Event Form. We will send the accelerometer for them to wear (and have it returned via mail).

Blood Pressure. Blood pressure will be assessed after a 5 minute rest period using a Dinamap Monitor Pro 100. Cuff size is determined by arm circumference. Three measures will be taken and averaged.

Laboratory Assessments. Blood samples will be taken for analysis of lipids (total cholesterol, HDL-C, LDL-C and triglycerides), glucose and insulin levels. Samples will be stored at -70 degrees and analyzed at the Northwest Lipid Metabolism and Diabetes Research Laboratory using standard procedures.

Anthropometric Measures. Weight will be measured in light clothes without shoes, on a calibrated scale, and height will be determined using a wall mounted stadiometer. Two measures of each are completed and the average of the two is used. If the two measures of weight differ by >.2 kg or height by >.5 cm, a third measure will be taken. The weight and height measures are used to calculate body mass index (weight in kilograms divided by height in meters squared). Waist circumference will be measured at the midpoint between highest point of iliac crest and lowest point of costal margin using a Gulik tape measure; two measures of waist circumference will be taken; if the difference exceeds 1.0 cm, a third measure will be taken.

Body Composition. Both sites will complete measures of body composition with the RJL Systems Quantum II impedance machine Three readings are taken, with a 30-sec wait between. In addition, participants at UNC also will have body composition assessed with the BodPod (COSMED USA, Inc).

Medications and Health Problems. Participants will report all prescription and non-prescription medications and indicate any health problems that they have experienced since the last assessment.

Objective Measure of Physical Activity. Physical activity will be assessed using an accelerometer to provide an objective assessment of physical and sedentary activity. Participants will be instructed to wear the device during all waking hours (except swimming and showering) for a full week; monitoring for at least 8 hours/day

and for at least 4 days in the week (including at least one weekday and one weekend day) which is considered adequate for analysis.

8.2.3 Questionnaires

We will continue to collect all questionnaire information remotely but distinguish below those measures collected every 6 months versus those collected annually and those only collected at Year 6. The questionnaires completed at 6 months will be used to compare the use of specific weight maintenance strategies and diet and physical activity behaviors over time in the three groups and to examine variables that are associated with subsequent weight changes.

8.2.3.1 Collected every 6 months

Diet Behaviors. Participants will complete specific questions assessing frequency of meals at fast food restaurants, frequency of meals at other types of restaurants, and consumption of sweetened beverages, [34] which have been related to weight gain in young adults.

Weight Management Strategies. SNAP-E assesses use of specific weight management strategies (e.g. record what you eat daily, cut out between meal snacking) compiled from Pound of Prevention, [11]NHANES and the Weight Loss Maintenance trial. Participants will be asked to indicate whether or not they have used each strategy within the past 6 months, and if so, to indicate how frequently they used the strategy. Participants also indicate whether they have participated in any other commercial weight loss programs including commercial and Internet programs and/or followed any other weight loss diets (e.g. Atkins).

Self-weighing. Frequency of self-weighing is assessed by asking participants how frequently they have weighed themselves within the past 6 months, ranging from several times a day, daily, a few times a week, weekly, once a month, or less than once a month to never.

Alcohol use. Questionnaires will be administered at each assessment to assess alcohol behaviors and any changes that occur over time.

Life Events. The life events questionnaire from the Coronary Artery Risk Development in Young (CARDIA) study lists 67 events and participants are asked to indicate whether or not that event has occurred in the past year.[34]

Perceived Stress. The Cohen Perceived Stress Scale[35] is a 4-item self-report instrument that captures the participant's perception of stress in their lives over the past month. The Perceived Stress Scale poses general questions about current stress levels. All items begin with the phrase: In the past month, how often have you felt…? This instrument has been used in many studies and has excellent reliability and validity.[35,36]

Quality of Life. All participants will complete the CDC Health-Related Quality of Life measure (commonly referred to as "Healthy Days Measures") at each assessment.[37] This 4 item questionnaire has been utilized in the BRFSS and NHANES and has been shown to have appropriate reliability, validity, and responsiveness to change.

Demographic Information. Data on occupation and education level will be updated. Gender, race/ethnicity, and ages collected during SNAP will be included in the database.

Contact Information, including contact information for the participant and 3 other contacts (used to locate participants) will be collected at each assessment visit in order to assist clinic staff with retention.

8.2.3.2 Collected annually (Years 5 and 6)

Physical Activity. The Paffenbarger Activity Questionnaire (PAQ) [38] will be administered as a measure of physical activity at each annual assessment visits. The PAQ has been used to assess leisure time activity in

many weight loss trials and can be scored to provide an estimate of calories expended per week in overall leisure time activity and in activities of light (5 kcal/min), medium (7.5 kcal/min), and high (10 kcal/min) intensity. Changes in exercise on the PAQ have been shown to be predictive of weight change in overweight and obese individuals.

Given the increasing recognition of the importance of sedentary activity, independent of physical activity, sedentary activity is assessed at each annual assessment visit using a self-report questionnaire, which asks respondents to indicate the number of hours they spend on a typical weekday and a typical weekend day doing a variety of sedentary activities.[39]

Medical Events and Pregnancy. Participants will be asked to provide information about recent pregnancies and adverse medical events or hospitalizations. Participants may be called for further information about these events if they represent possible safety concerns.

8.2.3.3 Collected only at 6 years

These measures were all completed at baseline, 4 months, and at 1, 2, 3 and 4 years follow-up of SNAP. They are included at Year 6 in SNAP-E to examine long term behavior changes and psychological outcomes across the 3 groups. Since some studies suggest that weight loss followed by regain is associated with negative psychological outcomes, [40] it is important to determine if the Large Changes approach produced any negative effects on these parameters.

Dietary intake**.** Dietary intake will be assessed at Year 6 using the Block Food Frequency[41] a food frequency questionnaire that has been used in a number of weight loss intervention trials including Look AHEAD and the Diabetes Prevention Program (DPP). For each food item on the Food Frequency, participants report the frequency of consumption and the portion sizes consumed over the past month. Although the Food Frequency measure will be completed at the same time as the Year 6 clinic exam, it will be done by participants on-line at their own convenience (as it has been done throughout SNAP).

Eating Disorders Assessment (EDA). Participants will complete a questionnaire used in Look AHEAD that assesses the frequency of binge eating episodes accompanied by loss of control, and the frequency of compensatory behaviors including vomiting, diuretics, and fasting.[42] These data will be used to identify any individuals who meet criteria for bulimia nervosa during the trial.

Eating Inventory. The Eating Inventory (TFEQ) [43] is a 51-item self-report instrument with three factors, assessing dietary restraint, disinhibition and hunger. The Restraint factor (range 0-21) assesses the degree of conscious control one is exerting over eating behaviors; The Disinhibition factor (range 0-16) measures susceptibility to loss of control over eating; and the hunger factor (range from 0-14) assesses hunger.

Smoking. Questionnaires will be administered to assess smoking and any changes that occur over time.

Sleep Habits. A questionnaire will be administered that asks about duration of sleep and problems encountered during sleep (e.g. snoring).

Neighborhood and Environment. A questionnaire will be administered t that asks about the neighborhood and environment and the facilities that are available.

Depression. The Center for Epidemiologic Studies Depression Scale (CES-D) [44] is a self-report depression scale designed to measure depression symptoms in the general population.

Treatment Satisfaction. Participants will complete a post-treatment process evaluation including describing the perception of the program. This information will provide a more complete picture of how the interventions are

perceived and experienced by young adults and may provide valuable information about how to modify the programs for future use in this population.

9. DATA MANAGEMENT AND QUALITY CONTROL

9.1 Data Management

SNAP has developed a web-based data management system that will be extended for SNAP-E. Custom server-side rules management logic and client-side JQuery interface technologies validate data entry and prevent data entry errors and facilitate step-through logic, skip-patterns, cross-form validation, and warnings. Client-side validation links directly to a customized Query Edit System. SAS is used for real-time data internet reports. Data are entered via an internet-based web browser interface with logic/error checks for staff to immediately correct errors. Confidentiality and data security are protected with using state-of-the-art https transmission protocols. The web site and web data entry forms are HIPAA compliant. Frequent off-site data backups permit disaster recovery.

9.2 Study Management

The SNAP-E system has customized collection and reporting tools to help clinic staff manage data collection. It includes customized tracking (e.g. adverse event reporting, intervention tracking) and quality control monitoring tools. The infrastructure knits highly customized web-based data management applications to relational database management and statistical analysis systems into a full featured project management system. Clinic and participant management tools have been developed to promote scheduling, retention reminders, and safety tracking.

10. PARTICIPANT MANAGEMENT AND SAFETY

10.1 Overview of Safety

Safety management in SNAP-E is intended to achieve five objectives: 1) to minimize the occurrence of adverse events, especially those related to interventions; 2) to effectively manage adverse events as they relate to the study; 3) to identify when SNAP-E interventions should be suspended because of concerns for participant safety; 4) to determine when interventions may be resumed after having been suspended; and 5) to provide information to the participant related to management of hypertension, dyslipidemia and other cardiovascular disease risk factors.

10.1.1 Definitions

Definitions are obtained from the “Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events Office for Human Research Protections (OHRP)” [http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm]. The requirements and processes of the National Heart, Lung, and Blood Institute are also implemented.

10.1.2 Medical Events and Serious Adverse Events

An adverse event is defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research. Abnormal laboratory results will be considered adverse events if they are not refuted by a repeat test conducted to confirm the abnormality or if the abnormality is of a degree that requires active clinical management.

Medical events and symptoms will be collected and reported from the beginning of study-related procedures to the end of the study follow-up period for an individual participant. Annually, SNAP-E staff will specifically query participants for medical events using the Medical Events form. Information on adverse events may also be reported to study staff during intervention contacts, as well as through telephone calls and emails, and will be recorded on the study interim event form. Specified Safety Alerts (see Table 2 below) will be followed until resolution, stabilization, or until it is determined that the study participation is not the cause. If there are any

positive responses on the Medical Events form, the form will be reviewed to determine if a Serious Adverse Event Form should be completed.

Consistent with NHLBI guidelines and OHRP policy, **serious adverse events** (SAEs) are adverse events that meet any of the following criteria: fatal or life-threatening, poses an immediate risk of death, result in significant or persistent disability that lasted at least 1 month and changed your life, requires an overnight stay in the hospital but NOT the emergency room, result in a congenital anomaly/birth defect, or are important medical events that investigators judge to represent significant hazards or harm to research subjects. Any adverse event that meets any of these criteria (e.g. results in hospitalization) will be documented and reported as a serious adverse event. The serious adverse event form will be completed by staff or investigators with the help of the participant who can provide information about the event.

10.1.3 Unanticipated Problems

An unanticipated problem is defined as any incident, experience, or outcome that meets **all** of the following criteria: 1) unexpected 2) related or possibly related to participation in the research; and 3) suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized. According to OHRP regulations, an incident, experience, or outcome that meets the three criteria for an unanticipated problem generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. Only a small subset of adverse events will be unanticipated problems.

10.1.4 Reporting of Serious Adverse Events and Unanticipated Problems

Selected serious adverse events will be reported to the Coordinating Center **within 24 hours** of knowledge of the event; these will include any deaths and serious adverse events that occurred on-site. The Coordinating Center will be responsible for timely reporting to the NIH, the OSMB, and other pertinent regulatory authorities. The Coordinating Center will provide reports of serious adverse events for review by the OSMB at its meetings.

If an adverse event that meets criteria for an unanticipated problem occurs at a SNAP-E site, the Principal Investigator of that site will promptly report the problem to their institution's IRB, as required by OHRP and NHLBI policy. Any event/problem that is fatal, life threatening or otherwise serious AND unexpected, AND definitely, probably or possibly related to study participation, will be reported to NHLBI within 7 calendar days. OHRP will be notified within 30 days.

10.2 Potential Risks to Study Participants

10.2.1 Potential Risks/Adverse Events Due To Study Participation

SNAP-E presents low risk to study participants, given the young age of the study population and the nature of the interventions and study measurements. Participants may experience faintness or bruising from the collection of the blood sample, while infection at the site is possible but rare. Weight loss may result in increased fertility which could increase the likelihood of becoming pregnant. Increasing physical activity may result in joint discomfort, muscle soreness, exacerbation of pre-existing hernia or musculoskeletal injuries, exacerbation of exercise-induced asthma, and new-onset minor injuries including sprains and fractures. Participants may not lose weight or may gain weight. Cholecystitis may occur with weight loss. Transient increases in the risk of sudden death and acute myocardial infarction occurring during a bout of vigorous exercise have been observed, especially in previously sedentary individuals, but these events are expected to be rare in young adults of the age range included. Adverse events that may occur with weight loss and increased physical activity, including fractures, sprains, acute asthma exacerbation requiring emergency care, and gall bladder problems will be carefully monitored and reported.

Given the age and weight range of this population, the greatest concerns are that participants may engage in unsafe dietary practices, lose weight more quickly or to lower levels than recommended, or develop untoward psychological reactions. Previous studies by Stice and colleagues[45,46] have shown that normal weight women, aged 18-29, who were placed on calorie restricted diets for 6 weeks and lost significant amounts of weight, had

decreases in bulimic symptoms relative to controls. Other weight gain preventions studies also indicate that participants in these programs increase their use of healthy weight control practices and decrease their use of unhealthy practices.

10.2.2 Anticipated Adverse Events In Young Adults

Adverse events, particularly serious events, not related to study participation are expected to be uncommon in this study of lifestyle intervention in generally healthy young adults. Nevertheless, young adults in this age range do experience acute health conditions and physical trauma that could result in serious adverse events, including disability, hospitalization and even death. Common causes of serious adverse events and/or hospitalization in this age range include mental disorders, digestive system diseases, unintentional injuries, genitourinary diseases, respiratory diseases, musculoskeletal diseases, endocrine diseases, neoplasm/cancer, diseases of the heart, pregnancy and pregnancy-related complications, and infections. Births with congenital anomalies also occur although rates are rare. Other adverse events that occur in young adults include the development or worsening of eating disorders (e.g. bulimia nervosa), spontaneous and elective abortion, asthma exacerbation, and various injuries. The most common causes of death in this age range in the US are unintentional injuries (accidents, homicide), intentional injury (suicide), malignant neoplasm's, diseases of the heart, congenital malformations, HIV disease, pregnancy/childbirth/puerperium, cerebrovascular diseases, diabetes mellitus, influenza/pneumonia, chronic lower respiratory diseases, chronic liver disease, and septicemia.

10.2.3 Minimization of Risks

The SNAP-E protocol and interventions are designed to minimize the occurrence of any untoward effects. All SNAP-E participants will again be advised about safe weight loss or maintenance practices including dietary change and increasing physical activity. Participants will be advised to gradually increase their physical activity and to use walking as a primary form of activity and will be taught that the appropriate rate of weight loss is 1 to 2 pounds per week. In addition, we will carefully monitor changes in weight during our trial. We will collect information annually on hospitalizations for any psychiatric problem, including depression and eating disorders, and provide these data to the Observational Study Monitoring Board (OSMB). We will track weight changes (using assessment data) and identify any individual who has a BMI of 18.5 kg/m^2 or below at any point during the program, or loses more than 20 pounds in any 6 month period during the trial. We will communicate with the participant within 2 weeks, discuss our concerns with them, and make referrals if appropriate. If there is no improvement in weight status, the participant will be unable to continue to participate in the interventions. However, we will continue to follow these individuals for outcome assessments.

Blood pressure will be measured in the clinic at the Year 6 assessment. We will use the JNC guidelines and inform any participant with Stage 1 hypertension (blood pressures of 140-159/90-99 mmHg) to be evaluated by their physician within 3 months; those with Stage 2 hypertension (blood pressures of 160-179/100-109 mmHg) to be evaluated by their physician with 1 month. If blood pressures >180/110 mmHg, participants will be advised to see their physician within 1 week or evaluated immediately depending on clinical situation and complications, based on a review conducted by a study clinician. We will also identify any participants with heart rate >110 bpm. These participants will be advised to see their physician within 1 month. All information about blood pressure and heart rate levels will be conveyed to participants verbally at the time of these measurements and in writing immediately after the visit with the above recommendations regarding contacting their physician. We will caution participants with elevated blood pressures about doing physical activity until they are able to have their blood pressures re-checked. Fasting glucose and lipid values will be obtained at Year 6. The results of these tests will be available within a month of completing the blood work and will be conveyed to participants in written format. If LDL-cholesterol levels exceed 160 mg/dl or triglycerides exceed 500 mg/dl, participants will be asked to contact their physician. If glucose levels are <60 or ≥126 mg/dl, participants will be informed of these values and given the option of having them repeated at our clinic or seeing their physician.

Table 2 summarizes the SNAP-E alert values and the action required.

Table 2. Alert Values and Action Required

ALERT	ACTION
Blood Pressure	Participants will be given the JNC VII blood pressure recommendations and follow-up guidelines at the clinic visit. Clinic staff will inform the participant at time of measurement.
Stage 1 hypertension SBP 140-159 OR DBP 90-99 mm/Hg	Participant advised to see a health care provider within 3 months
Stage 2 hypertension SBP 160-179 OR DBP 100-109 mm/Hg	Participant advised to see a health care provider within 1 month
Stage 3 hypertension SBP ≥ 180 OR DBP ≥ 110 mm/Hg	Participant advised to see a health care provider within 1 week or immediately
Heart rate > 110 bpm	Clinic staff will inform the participant at time of measurement. Participant advised to see a health care provider within 1 month
Lab Values	Notify participants within 1 month of receiving lab values
LDL > 160 Triglycerides TG ≥ 500 mg/dl	Participant advised to see a health care provider within 1 month
Glucose < 60 or ≥126 mg/dl	Participant given the option of going to their physician or re-checking in clinic; if abnormal on re-check, inform participant to see a health care provider within 1 month
Excessive weight loss BMI $\leq$ 18.5 kg/m^2 or loses more than 20 lbs within a 6 month period	Telephone the participant to counsel, within 2 weeks. If participant remains below 18.5 kg/m^2 or continues to lose more weight, intervention activities will stop.
Eating Disorder/Eating habits	If a participant develops Bulimia Nervosa during the course of the trial (i.e., they meet full diagnostic criteria for BN at any follow-up assessment), we will temporarily discontinue intervention until the participant is healthy. A qualified staff member will meet with the participant individually and counsel them to seek professional treatment, and a list of referrals and/or a community resource guide will be provided. The participant will need medical consent / clearance before resuming treatment in the current study.

We will also monitor any major musculoskeletal problems that develop during the intervention (e.g. broken bones) and determine whether these appear related to our intervention. Participants who develop musculoskeletal problems or other health problems that may affect the safety of the intervention will be instructed to stop exercising until the problem resolves and their physician approves the resumption of physical activity.

Since young adults are targeted in this trial, we expect that pregnancies will occur. We will advise pregnant participants to consult with a physician prior to completing any intervention activities. However, at 6 months post-partum, we will encourage participants to return to the intervention and the assessments for this trial.

All participants will be given access to the study website using a unique username and password to protect confidentiality. Weights collected via the Smart-Scale will be transmitted via the cellular network. The serial number of the Smart-Scale will be used to link this data to the participant.

All key personnel will have attended the required courses on human subject protection and HIPAA regulations, and certificates of IRB completion are on file with the Miriam Hospital, the University of North Carolina, and Wake Forest University Health Sciences. All participants will sign an Informed Consent Form that has been approved by the Institutional Review Boards at the Miriam Hospital and the University of North Carolina, and Wake Forest University Health Sciences. In addition we will comply with all HIPPA regulations.

10.3 Monitoring

The SNAP-E Observational Study Monitoring Board (OSMB) will review study progress and productivity twice a year.

11. ANALYSIS PLANS

Analyses specified in the SNAP protocol to meet its objectives will be conducted at its conclusion. The goals of SNAP-E are distinct from those of SNAP; analytical plans to address these are as follows. We will begin by carefully assessing differences between SNAP-E enrollees and the original SNAP cohort. While SNAP retention has been excellent, some lost follow-up will have occurred and additional losses are likely to occur during SNAP-E enrollment. In other trials, these losses are differential, i.e. are more frequent among subgroups of participants.[47] Of critical importance will be to understand if they are differential among intervention groups and whether, with appropriate covariate-adjustment, they can be assumed missing at random.[48] If so, likelihood-based to SNAP-E analyses will be valid.

For the primary aim of assessing weight changes (from SNAP baseline) at Year 6, analyses will be based on generalized linear models[49]in which all weight changes from assessments during SNAP and SNAP-E are included in analyses (with a covariate term to indicate whether these are clinic-based or collected via Smart-Scales) and linear contrasts are used for estimation and inferences related to SNAP-E goals. These will be used to assess the 3 pairwise comparisons between intervention groups at Year 6 (with Bonferroni adjustment to control type 1 error). Weight changes at 4 months, 1, 2, 3, 4, and 6 years from baseline, which are clinic-based weight measurements, will be first analyzed using the mixed effects model. Effects of treatment group, time, and group by time interaction will be examined. Randomization stratification factors including clinic site, gender, and race (Non-Hispanic White vs. others) will be adjusted in the model as covariates. Various dependence structures, such as unstructured or auto-regressive, will be examined and the likelihood ratio test will be used to determine the best fitting one. The main effect of treatment group will be assessed at 5% significance level. Three linear contrasts comparing pairwise group differences (LC vs. Control, SC vs. Control, LC vs. SC) in the mean weight change from baseline to 6 years will be estimated and tested using the Wald's statistic at 1.67% significance level.

Secondary analysis will include weights collected via Smart-Scales at 4.5, 5, and 5.5 years. Weight changes at these additional 3 time points will then be calculated. Along with clinic-based weight measurements, weight changes at 4 months, 1, 2, 3, 4, 4.5, 5, 5.5, and 6 years from baseline will be analyzed using a separate mixed effects model similar to the one specified above, adding a covariate term indicating whether these are clinic-based or collected via Smart-Scales. Inference for the main effect of treatment group will be conducted at 5% significance level and the Bonferroni adjustment will be made for the three linear contrasts for pairwise comparisons.

Similar approaches will be used for the secondary outcomes of changes from baseline in body composition measures, glucose, insulin, and lipid levels. We will compare the proportion of participants who have transitioned from baseline to overweight or obese at Year 6 using logistic regression. In supporting analyses, we will also use generalized estimating equations and Markov models to compare the transition rates among weight classes over time for the intervention groups. Similar approaches will be used for changes in the use of weight control strategies. Changes in dietary and physical activity measures and in the frequency of self-weighing, at Year 6 and over time, will be analyzed using separate mixed effects models.

The exploratory aims related to inter-relationships among changes in behavior, weight, and health outcomes will be addressed through the use of time-varying covariates in repeated measures models and by examining inter-correlations.

We will use two approaches to assess the sensitivity of our results to the missing at random assumption. With multiple imputation[50] we will create 5 randomly augmented (i.e. completed) databases and average the results of analyses on each. We also will use inverse propensity approaches[51] with weighted analyses to adjust for missingness. We will report the results of these supporting analyses in our primary publications. In the Markov models described above, we will also include lost follow-up as an absorbing state to assess the impact of missing data on findings.

There is considerable heterogeneity in weight trajectories between groups and among participants within groups, which is a rich source of information. We have experience with the two primary approaches towards examining patterns of weight changes, using 1) investigator-defined classification (e.g. weight gain, stable, maintained loss, regain)[52]or 2) empirically-derived characterizations (e.g. based on latent class analyses, pattern decomposition, and clustering).[32,53] In supporting analyses, we will apply both to the trajectories of weights among SNAP-E participants. We will group participants according to the above investigator-defined classifications, examine how these groups vary among intervention assignments, and identify factors (see subgroups below) associated with group membership. We will also use principal components analyses to decompose weight loss trajectories into predominant features and examine how these features vary among intervention groups and are related to participant characteristics.

We will determine whether baseline variables moderate the intervention outcomes. Our analysis plan will pre-specify subgroups across which we will examine the consistency of any intervention effects using tests of interaction. For SNAP, we have pre-specified these subgroups to be based on baseline BMI, race/ethnicity, age, scores on the Eating Inventory, and baseline treatment preference. For SNAP-E, we will add gender. Accruing weights every 6 months via the remote technology allows us to consider other sources of variation between and within groups. For example, we will be able to determine whether there are differences in the probability of recovering from small weight gains (defined as gains of 3% or more.[54] We will also determine whether young adults gain weight steadily over time or with periodic, larger weight gains, and whether these occur in response to specific lifestyle changes (pregnancy, marriage).

Our analysis plans will also describe assessments of mediation, i.e. factors that are intermediate to outcomes, such as changes in diet, physical activity, restraint, and self-regulatory behaviors. We are particularly interested in determining whether self-monitoring of body weight mediates the effects of the two interventions, since both are based on self-regulation. Analysis of mediation will include traditional models for mediation of continuous, categorical, and multivariate mediators.[55-57] These approaches make many simplifying assumptions. In supporting analyses, we will fit more realistic models of mediation, applying latent variable and Bayesian methods to outcomes and weight trajectories.[58,59]

Mediation analyses will be conducted by fitting a series of 3 regression models. In model 1, weight change from baseline to year 6 is regressed against the treatment group to establish direct effect of the intervention on weight change. In Model 2, we will regress each potential mediator (self-monitoring of body weight, changes in diet, physical activity, restraint, and self-regulatory behaviors) against the treatment group. In model 3, weight

change is regressed against both treatment group and potential mediators. A significant treatment effect in model 2 and a significant effect of potential mediators in model 3 constitute an indirect effect of intervention on weight change from baseline to year 6 through potential mediators. Significance of the indirect effects, both overall combined and separately as each indirect path will be assessed using the bootstrap method. Confidence intervals will be constructed and we will check to see if the value of zero is included in these confidence intervals. Relative strength of these indirect paths can also be evaluated by using contrasts. The SAS macro %PROCESS will be used to conduct mediation analyses.

We will assess the potential of using remote weight measurement technology: data completeness their alignment with the clinic-based measures. We will examine for discontinuities in trajectories (using markers to denote the mode of assessment) to estimate biases and will also compare the variances and longitudinal correlations. We will describe the viability of retaining young adults in a trial with infrequent clinic visits, using similar methods. For both these aims, we will look at the consistency of findings among important clinical groups, using tests of interactions. Our goals will be to provide benchmark data for the efficient design of large-scale cost-efficient simple trials of weight loss interventions that do not require clinic assessments.

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