HHS Public Access

Author manuscript

Contemp Clin Trials. Author manuscript; available in PMC 2020 September 01.

Published in final edited form as:

Contemp Clin Trials. 2019 September ; 84: 105824. doi:10.1016/j.cct.2019.105824.

Design of the PACIFIC study: A randomized controlled trial evaluating a novel treatment for adults with overweight and obesity

Kerri N. Boutelle[a,b,c,*], **Dawn M. Eichen**[a], **Carol B. Peterson**[d], **David R. Strong**[b], **Cheryl L. Rock**[c], **Bess H. Marcus**[e]

[a]Department of Pediatrics, University of California San Diego, 9500 Gilman Drive, La Jolla, CA, 92037 USA

[b]Department of Family Medicine and Public Health, University of California San Diego, 9500 Gilman Drive, La Jolla, CA, 92037 USA

[c]Department of Psychiatry, University of California San Diego, 9500 Gilman Drive, La Jolla, CA, 92037 USA

[d]Department of Psychiatry, University of Minnesota, F282/2A West 2450 Riverside Ave, Minneapolis, MN 55454, USA

[e]Department of Behavioral and Social Sciences, Brown University, School of Public Health 121 South Main Street, box G-S121-3, Providence, RI 02912-G, USA

Abstract

The majority of adults in the United States have overweight or obesity which is associated with significant health and psychological consequences. Behavioral Weight Loss (BWL) is the current gold-standard weight loss program for adults but recidivism rates continue to be disturbingly high. Given the health consequences of excess weight and the lack of long-term effectiveness of BWL, it is important to identify novel weight-loss programs. We developed the ROC (Regulation of Cues) program to reduce overeating through improvement in sensitivity to appetitive cues and decreased responsivity to external food cues. This study is a 4-arm randomized control trial designed to evaluate the efficacy of ROC, ROC combined with BWL, BWL alone and an active comparator over 24 months. Study recruitment completed in November 2017. Two hundred and seventy-one participants were randomized (mean age=46.97 years; 82% female, mean BMI=34.59; 20% Hispanic) and assessments were conducted at baseline, mid-treatment (6 months) and post-treatment (12 months). At this time, participants are completing 6- (18 months) and 12-month (24 months) follow-ups. Targeting novel mechanisms is critically important to improve weight loss

[*]Corresponding Author: Kerri Boutelle: 9500 Gilman Drive, MC 0874, La Jolla, CA, 92037, kboutelle@ucsd.edu, phone: 858-534-8037.

Conflict of Interest:

Dr. Boutelle has received research funding from the Egg Nutrition Board.

programs. Through this trial, we hope to identify treatments for adults with overweight and obesity to facilitate long-term weight loss and improved health.

Keywords

Weight loss; Binge Eating; Regulation of Cues; Behavioral Weight Loss

1. Introduction

Behavioral Weight Loss (BWL) is considered the standard behavioral treatment for weight loss among adults with overweight and obesity.(1–3) BWL provides a lifestyle intervention consisting of dietary recommendations, physical activity guidelines, and behavioral techniques. The ultimate goal of BWL is to lose ≥ 7% of initial body weight.(4) For some adults, BWL is effective, yielding clinically significant weight loss. On average, participants in BWL lose 8.6% of their total body weight at the end of a 12-month program, which equates to approximately 7–10 kilograms of body weight.(5) However, regaining lost weight after BWL continues to be incredibly common,(6) suggesting that there are underlying mechanisms unaddressed by BWL which could impact long-term treatment effectiveness.

We have developed a new model for the treatment of obesity called Regulation of Cues (ROC), which is based on the behavioral susceptibility theory of obesity (BST).(7–9) The BST states that individual characteristics in appetitive traits are genetically determined and influencers of how an individual interactions with the current food environment. The BST highlights the importance of both eating onset (responsiveness to signals to start eating, i.e. food responsiveness (FR)) and eating offset (responsiveness to signals to stop eating, i.e. satiety responsiveness (SR)). This dual-susceptibility was first described by Stanley Schachter in the 1960s whose Externality Theory hypothesized that individuals with overweight/obesity are more reactive to external cues to eat and less sensitive to internal satiety signals than their lean counterparts.(10, 11) The ROC program uses psychoeducation and an experiential learning approach to promote proactive management of external cues for eating onset and by increasing sensitivity to internal cues for eating offset. Our pilot data suggest that influencing these appetitive behaviors offers a promising approach for weight-loss among adults who binge eat(12) as well as for children with overweight and obesity.(13, 14) We believe that by targeting these proposed mechanisms of overeating, we can potentially develop more durable and long-lasting weight-loss for adults with overweight and obesity.

2. Study objectives

In the PACIFIC (Providing Adult Collaborative Interventions for Ideal Changes) trial, 271 adults with overweight or obesity were randomly assigned to one of four group-based conditions: Regulation of Cues (ROC), Behavioral Weight Loss (BWL), a combined treatment (ROC+), or a structured series of informational sessions (e.g. nutrition, stress management and social support) that served as an Active Comparator (AC). All treatments lasted 12 months and planned outcome assessments at 6- and 12-months after treatment are underway. The primary aim of the study was to evaluate whether interventions led to

differential changes in body mass index (BMI), and binge eating. Additionally, we included measurements of the hypothesized mechanisms of change in these programs.

3. Study design

3.1. Trial design

PACIFIC is a parallel group, randomized controlled trial for adults with overweight or obesity with four arms: ROC, ROC+, BWL and AC. Assessments will be conducted at five time points: baseline, mid-treatment (month 6), post-treatment (month 12), 6-month follow-up (month 18) and 12-month follow-up (month 24). The primary outcome measures are body mass index (BMI), and binge eating over the course of treatment and follow-up assessments. Secondary outcomes include sensitivity to appetitive cues, reactivity to external food cues, inhibitory control when exposed to food cues, dietary restraint, energy intake, overeating, and physical activity.

3.2. Participants

Participants in the study are 271 non-diabetic men and women with overweight or obesity (mean BMI = 34.59; mean age = 46.97; 82% female; 20% Hispanic) who were recruited, enrolled, and randomized to one of the four arms.

3.3 Inclusion/Exclusion criteria

Participants were enrolled with the following criteria: Aged 18–65 years; BMI ≥25 kg/m^2 and ≤ 45; English language skills at the 5^{th} grade reading level; willing and able to participate in assessment visits and treatment sessions; and willing to maintain contact with the investigators for 24 months. Exclusion criteria included history of bariatric surgery, recent history of coronary heart disease; recent history of myocardial infarction; recent symptoms of angina, diabetes, recent stroke, orthopedic problems that would limit activity during the following 12 months; or any other serious medical condition that would make physical activity unsafe. Other exclusion criteria included concurrent participation in another organized weight control program or use of medication for weight loss, planning to move from the area within the next two years, current suicidal ideation, psychosis, current substance abuse or dependence, current pregnancy or lactation, hospitalization due to a psychiatric disorder in the past year, and/or taking medication that may impair physical activity tolerance or performance. Participants with medical or psychological problems that could make adherence with the study protocol difficult or dangerous were excluded.

3.4. Recruitment and retention

Participants were recruited from the San Diego Metropolitan area using online advertisements such as social media ads (e.g., Facebook and Instagram), flyers to physicians, flyers posted on campus, radio ads, ResearchMatch, and professional referrals to the center from local physicians. Participants who responded to recruitment efforts completed an online screen to determine initial eligibility. Participants who met study inclusion criteria completed a phone screen to further assess eligibility. If participants met initial screening criteria, they attended an orientation to learn more about the study. If they were interested in participating after the orientation, participants signed an informed

consent, had their anthropometrics measured to ensure qualification and completed baseline assessments. Recruitment occurred between December 2015 and November 2017.

Several strategies were used to maximize participant retention. During treatment, study interventionists offered make-up sessions when participants were unable to attend, either over the telephone or in clinic. If a participant missed a session without prior notification, the study interventionist emailed the materials and called the participant to schedule a make-up session. We also requested contact information for two close friends or relatives to further enhance our ability to locate participants.

3.5. Assessment and outcome measures

All measurements along with corresponding time points are listed in Table 1. Participants complete five assessments: baseline, mid-treatment (month 6), post-treatment (month 12), 6-month follow-up (month 18) and 12-month follow-up (month 24). Assessments include anthropometry, self-report questionnaires, tasks and structured clinical interviews. Data collection is being conducted by trained staff and supervised by licensed clinical psychologists. Initial baseline assessments began in December 2015 and the final 12-month follow-up data collection is scheduled to occur in November 2019.

3.6. Measures

3.6.1. Anthropometry

Body Mass Index: Height is measured using a portable Schorr height board (Schorr Inc, Olney, MD) in triplicate. Height is recorded to the nearest 0.1 cm for all trials, and the average of the three values will be used for analysis. Body weight in kilograms is measured on a calibrated Tanita Digital Scale (model WB-110A) and is recorded to the nearest 0.1 kg. Participants removed their shoes for height or weight measurements. Height and weight are converted to body mass index (BMI=[kg/m^2]).

Body Composition: Body composition was measured with dual-energy x-ray absorptiometry (DXA). Due to budgetary restrictions, only participants in the first two waves completed DXA scans and thus will be analyzed in an exploratory manner. Scans were conducted by experienced technicians certified in the state of California and were processed using CoreScan/encore Software (GE/Lunar, Madison, WI, USA).

3.6.2. Medical and Psychiatric History (screening only)

Medical history and current medication use: During initial screening, a research staff member inquired about current medications and the presence of medical conditions that could interfere with treatment. Participants reported any changes in medical status and medications throughout treatment and at follow-up. This information is used for eligibility purposes only, both at screening and throughout enrollment.

Mini International Neuropsychiatric Interview version 6.0 (MINI).(15): The MINI is a structured clinical interview used to assess psychiatric diagnoses, based on diagnostic categories from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). Trained interviewers administered the MINI at baseline to determine the presence of a

psychiatric disorder warranting study exclusion. The MINI has demonstrated adequate reliability and validity.(15) Interviewers were certified and supervised by a licensed clinical psychologist.

3.6.3. Binge Eating and Eating Disorder Symptoms

Eating Disorder Examination (EDE version 17.0).(16, 17): The EDE is a structured clinical interview that assesses disordered attitudes and behaviors related to eating, body-shape and weight, and eating disorder symptoms defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Trained interviewers administer the diagnostic items from the EDE interview to evaluate eating and compensatory behaviors and patterns of eating, including binge eating. The EDE is administered at all assessment time points and was used to exclude adults meeting criteria for bulimia nervosa, and to determine the presence and number of episodes of binge eating across the study time period. Data support the reliability and validity of the EDE.(18) Interviewers were certified and supervised by a licensed clinical psychologist.

Eating Disorder Examination Questionnaire (EDEQ; version 6.0).(19): The EDEQ is a questionnaire adaptation of the EDE interview and is used to assess eating disorder attitudes and behaviors at each assessment time point. The EDEQ has strong psychometric properties.(18, 20) During treatment, the self-report binge eating items and the dietary restraint subscale were administered monthly to evaluate change over treatment.

Binge Eating Scale (BES).(21): The BES is a 16-item questionnaire that assessed binge eating severity in a continuous manner. The BES demonstrates significant validity in identifying loss of control over eating but is less precise at differentiating between large or small amounts of food.(22)

3.6.4 Sensitivity to Appetitive Cues

The *Intuitive Eating Scale – 2 (IES-2)*.(23): The IES-2 is a 23-item questionnaire that measures a participant's tendency to eat in response to physical hunger and their body's needs. The measure creates an overall score and four subscales: Unconditional Permission to Eat, Eating for Physical Rather than Emotional Reasons, Reliance on Hunger and Satiety Cues, and Body-Food Choice Congruence. The IES-2 has high validity and internal consistency.(23)

3.6.5 Reactivity to External Food Cues

Power of Food scale (PFS): The PFS(24) is a 15-item questionnaire that assessed an individual's drive to consume highly palatable foods. The measure creates an overall score and three subscales: Food Available, Food Present, Food Tasted. The PFS has strong internal consistency and adequate test-retest reliability.(24, 25)

Heart Rate Variability: We developed a controlled laboratory-based assessment protocol to evaluate psychophysiological responses to food cues. Participants undergo six minutes of baseline data collection, then six minutes of exposure to their preferred standardized food, followed by six minutes of recovery (food is removed). All measurements are taken using a

BIOPAC MP150 model (BIOPAC Systems, Inc.) with electrophysiological recordings sampled at 1,000 Hz. HRV was chosen as a measure of Cephalic Phase Response (biological preparatory responses to food) and has shown sensitivity to conditioning paradigms with food.(26) Prior to conducting the task, participants are asked to rate a standardized list of eight foods: Lays Potato Chips, Fritos, Cheez-Its, Chocolate Chip Cookie, Hershey Kisses, M&Ms, Gummy Bears, Blueberry Muffins. The top-rated food is chosen for the task. During the exposure, participants are instructed to look at the food for 30 seconds and rate their craving on a level of 1–5, then smell the food for 30 seconds and rate their craving, alternating between looking and smelling the food while rating cravings every 30 seconds for the duration of the six minutes. Heart rate (HR) and heart rate variability (HRV) will be measured continuously during the food exposure tasks.(27)

3.6.6 Inhibitory control in response to food cues

Stop Signal Task with food stimuli: The stop signal task evaluates motor impulsivity. An adapted version utilizing food stimuli was used to assess food-specific motor impulsivity. Participants are shown pictures of highly palatable foods and neutral stimuli. Participants are instructed to press “C” if the picture was a food and “M” if it was not as quickly as possible. However, if a border appeared (stop trial; 25% of trials), participants are told that they should not press anything. The speed at which the stop signal is presented is adjusted based on the participant’s accuracy. A Stop-Signal Reaction Time (SSRT) using the integration method will be calculated with slower SSRTs indicating taking more time to stop one’s response suggesting greater impulsivity.(28, 29)

3.6.7 Dietary Restraint

Three Factor Eating Questionnaire – Restraint subscale (TFEQ) (30): The TFEQ-Restraint subscale assesses dietary restraint over eating and is 21 items. The TFEQ has been shown to be psychometrically sound.(30, 31)

3.6.8 Energy Intake

Dietary History Questionnaire–II (DHQ-II).(32): The DHQ-II is a food frequency questionnaire that assesses consumption of 134 food items and 8 supplements.(33) The DHQ-II version evaluates food consumption over the past month and assesses portion size. The DHQ-II will be analyzed using the Diet*Calc software developed by the National Cancer Institute and provides nutrient and food group estimations including a measure of energy.(34)

3.6.9 Overeating

Eating in the Absence of Hunger Questionnaire for adults (EAH-A): EAH-A was adapted from the Eating in the Absence of Hunger Questionnaire for Children and adolescents (EAH-C).(35) EAH-A is a 14-item questionnaire that measures tendencies to eat past satiation during a meal and tendencies to start eating despite not being hungry. The original factor analysis produced three subscales: negative affect, external eating, and fatigue/boredom eating.(35)

3.6.10 Physical Activity

Physical Activity Recall (PAR).(36): The 7-Day PAR is a semi-structured interview that assessed weekly minutes of physical activity. Participants report their time spent in moderate, hard, and very hard intensity for ≥ 10 minutes continuously.(37) The PAR is validated and has shown acceptable reliability and sensitivity to change in physical activity over time.(36–38) Interviewers were trained and supervised by a licensed clinical psychologist.

Godin Leisure-time exercise questionnaire.(39): The Godin Leisure-time Exercise questionnaire assesses the number of times per week individuals participate in strenuous, moderate or mild exercise for more than 15 minutes during leisure time. The Godin also assesses whether participants work up a sweat often, sometimes or never/rarely in a week. This measure is related to objective measures of physical fitness and exercise and is a reliable and valid measure of leisure-time exercise.(40)

3.6.9. Additional measures of treatment adherence—In addition to pre and post-treatment assessments, adherence and attendance data were obtained weekly during the treatment program. Attendance was recorded by group leaders and adherence to self-monitoring was measured by collecting weekly self-monitoring from participants in the ROC, BWL and ROC+ treatments.

3.7 Assessment procedures

Baseline assessments were discussed in a weekly consensus and supervision meeting led by clinical psychologists to determine whether or not individuals met inclusion criteria. Assessors described findings from the clinical interview that may have warranted study exclusion (e.g., significant depressive symptoms). When individuals reported symptoms that could likely interfere with study participation, safety, and engagement (based on study exclusion criteria), they were excluded from the study after consulting with the PI. Examples of this included severe depression, current suicidal ideation, or compensatory behaviors (i.e. purging).

3.8 Intervention

Individuals were randomly assigned to one of four conditions:

ROC, BWL, ROC+ and AC (nutrition, stress management and social support) stratified by gender and endorsement of loss of control (yes/no) on the EDE. All randomized participants attended group treatment that included 26, 90-minute visits over 1 year. Groups met weekly for the first 16 weeks, twice a month for 2 months and monthly for 6 months. All four group treatments included a mix of didactic teaching, discussion, and activities. Key differences between the treatment arms are outlined in Table 2 and are described below.

3.8.1 Regulation of Cues (ROC)—As described above, our treatment model, called Regulation of Cues (ROC), is based on the behavioral susceptibility theory of obesity and Schachter's externality theory. We have tested this model in children(13, 14) and adults.(12)

ROC includes psychoeducation, coping skills, experiential learning, self-monitoring and physical activity.

Psychoeducation: The ROC program provided psychoeducation at each group visit by describing a "Tricky Hunger", which was defined as a way that the environment "tricks" the body into overeating past nutritional needs. The overall goal of psychoeducation was to increase participant's awareness of the situations, thoughts, moods, and environments that lead to overeating. Psychoeducation was designed to reduce guilt regarding overeating by helping participants understand the biological and psychological processes by which these phenomena occur. Rather than avoiding the negative emotions associated with overeating, understanding the reasons and situations that drive overeating could improve deployment of self-regulation skills. A model for influencing overeating behavior was introduced that included the importance of attention/sensitivity to hunger/satiety cues and increased attention/sensitivity to food cues. Physiological, neurobiological and environmental models of overeating past nutritional needs were presented in lay language so that participants could understand how these vulnerabilities may lead to overeating. Participants were provided information about basic learning theory and how physiological responses to food cues develop and can be managed.

Coping skills: Coping skills were taught to identify and manage any instances of Tricky Hunger. Coping skills were presented to assist in mastery and tolerance of food cue sensitivity. Coping skills included physiological skills (deep breathing, relaxation, mindfulness), behavioral skills (delay, activity substitution) and cognitive skills (cognitive restructuring, distraction).

Experiential learning and self-monitoring: In each session, participants completed an experiential learning exercise. During visits 2–8, participants were instructed about hunger and satiety dysregulation. Participants were taught to self-monitor their hunger, either in a self-monitoring booklet or an app, on a 1–5 scale, with 1="starving" and 5="stuffed". Participants were instructed to self-monitor hunger and satiety before, during and after each meal, as well as 20 minutes after eating for a minimum of two meals/snacks per day. Participants brought dinner to groups where they ate dinner and monitored their hunger at the beginning of each group. Conditions were manipulated to simulate eating under different conditions (boredom, sadness, when full, when hungry).

During visits 9–16, participants learned to assess and rate their cravings (defined as urges to eat when not physically hungry). Craving was monitored with a 5-point scale, 1= "not craving it at all" and 5= "craving is overwhelming" and participants rated cravings during the day (ideally one craving a day at minimum). Participants created a craving hierarchy and brought their own highly craved foods to group. Using their highly craved foods, they completed two exposures at each session (starting at session 10; CET-Food) when physically sated with their preferred foods. If the participant was physically hungry, they ate a snack before participating in an exposure. During the exposure, participants rated their cravings while looking at the food, holding the food, smelling the food, after taking two small bites of the food, and rated their cravings at 30-second intervals for the duration of the exposure. After 5 minutes, the participants disposed of the food without eating it.

3.8.2 Behavioral Weight Loss (BWL)—The BWL program included dietary recommendations, physical activity recommendations, and behavioral change recommendations.

Dietary recommendations: All participants were instructed to consume a balanced deficit diet of conventional foods that provided ~15–20% of energy from protein, 30% or less energy from fat, and the remainder from carbohydrate. Individual goals for energy intake were based on body weight. Each week participants were provided an ideal range and encouraged to set an individual goal. The range was calculated by multiplying the participant's weight in lbs × 12 to get the amount of calories needed to maintain current weight and subtracting 500 and 1000 calories to create a range where anticipated weight loss would be 1–2 lbs/week. Nobody was ever instructed to consume less than 1200 calories and if a participant's weight increased, he/she maintained the previous week's range. Participants were instructed in measuring portion sizes, counting calories (with a calorie counter provided or on their phone), and self-monitoring food intake.

Behavior change recommendations: Behavior change recommendations include stimulus control, self-monitoring, goal setting, managing high-risk situations, meal planning, slowing eating, problem solving, social support, cognitive restructuring relapse prevention skills, and skills for maintaining weight loss. Participants self-monitored their physical activity, step counts and food intake daily.

3.8.3. ROC+—BWL and ROC were integrated to capitalize on the strengths of both treatments. Participants were taught to decrease caloric intake and increase physical activity, and to use all of the behavioral skills provided in BWL. In addition, the ROC model featuring roles for hunger and satiety when learning cues for food were introduced along with skills for managing satiety responsiveness and food cue responsiveness. This arm included all of the ROC experiential components. Participants in this group also were provided with standard materials to conduct self-monitoring of food intake, hunger, cravings, physical activity and daily steps.

3.8.4 Active Comparison (AC)—The timing and number of sessions for the AC was matched to the other treatments. However, AC treatment components were purposefully independent of the ROC and BWL components. The prescribed psychoeducation topics included nutrition, stress management and social support. Participants were provided information about reading food labels and different "fad" diets. Participants were provided psychoeducation about how stress leads to weight gain as well as mindfulness-based stress reduction, sleep hygiene, and time management. Participants were provided with assertiveness training along with conflict management skills and were encouraged to build positive support networks. At each session, a mindfulness exercise was provided and participants were encouraged to practice mindfulness at home.

3.8.5 Physical Activity Across All Groups

Physical activity: Participants in all four groups were provided the same goal of engaging in at least 150 minutes of moderate or greater intensity physical activity. In the AC, physical

activity was encouraged to promote general health and stress management. In the ROC and ROC+ groups, physical activity was recommended to improve the self-regulatory strength needed for mastering and tolerating physiological and psychological arousal, resisting cravings and preventing overeating. In the BWL and ROC+ groups, physical activity was encouraged to burn calories and aid in creating a calorie deficit. Physical activity goals and strategies were kept consistent across ROC, BWL, and ROC+. Participants in these three groups were provided a pedometer and encouraged to achieve at least 10,000 steps per day. Participants used their booklet or app to self-monitor their physical activity and daily step count each day.

3.9. Treatment fidelity

Group interventionists for the PACIFIC program were registered dieticians, Ph.D. level postdoctoral fellows, advanced graduate students in clinical psychology and licensed clinical psychologists. All interventionists completed a day-long training course in their assigned treatment and attended regular supervision.

4. Statistical analyses

4.1 Sample Size and Power Considerations

We determined sample size for a four-group design to evaluate the primary hypotheses of the efficacy of ROC and ROC+ when compared with AC (PA1) and ROC and ROC+ when compared with BWL (PA2). The sample size was selected to ensure that the study would be expected to detect improvements over AC using effect sizes reflecting a range of standardized mean (Cohen's d) decrease in BMI d=−0.52–0.85 for ROC and ROC+, a moderate and clinically significant change (~5% decrease). Effect estimates for evaluation of mechanisms of treatment were informed by observed significant changes in binge eating behavior during pilot treatment with ROC (range of standardized mean difference using Cohen's d= −0.66 – 0.70(12)). Those reporting more change in binge eating during ROC treatment reported greater likelihood (OR=2.14, 95%CI=0.40–11.51) of maintaining or continuing weight loss after treatment (38% vs 78% maintain/reduce BMI from 3- to 7-months), supporting the potential indirect effect of ROC on reductions in BMI by impacting binge eating.

Empirical power estimates were assessed by generating multivariate random samples of four outcome measurements that were matched to the expected BMI for each condition using the same correlation structure of assessments over time as observed in our pilot study. The percentage of datasets with effects that were significantly unlikely to have occurred ($p<0.05$) if the null hypothesis were true (i.e. there were no differences in BMI changes for participants in ROC, ROC+, BWL, and AC), provided a simulation-based estimate of power. With standardized mean treatment effects of −0.62 (ROC and ROC+ vs BWL $sd_{\text{effect parameter}}= 0.14$) and −0.30 (ROC and ROC+ vs AC $sd_{\text{effect parameter}}=0.09$) across 1000 data sets, the planned design of 70 per group (total n=280) would provide greater than 0.83 power for detecting the planned treatment comparisons with allowance for up to 20% lost to follow up. Empirical power analyses suggested that this sample also will sustain power >0.80 when exploring meditational hypotheses with an expected medium to large effect of

ROC and ROC+ on primary mediators (sensitivity to appetitive cues, reactivity to external food cues, inhibitory control when exposed to food cues, dietary restraint, overeating and binge eating) and medium effects of primary mediators on changes in BMI.(41) The proposed sample will allow moderation analyses (e.g. treatment by baseline binge status) with moderate to large effects to sustain power >0.81.

4.2 Data analyses

Primary outcomes—Analyses will use linear mixed effects (LME) models and will include comparison of ROC and ROC+ with AC interventions on changes on BMI and binge eating at mid-treatment, post-treatment, 6- and 12-month follow-up assessment after baseline (PA1). These LME models will include contrasts to simultaneously compare ROC and ROC+ to BWL on these target outcomes (PA2). Analyses of the secondary aim with LME or generalized LME will evaluate planned treatment group comparisons on changes in sensitivity to appetitive cues, reactivity to external food cues, inhibitory control when exposed to food cues, dietary restraint, energy intake, overeating, and physical activity (moderate/vigorous minutes/week) (SA1). All other study endpoints including behavioral and psychological outcomes are considered exploratory. Planned covariates will include gender, baseline binge eating status, and baseline values for assessing corresponding primary outcomes (PA1, PA2).

Exploratory Analyses: We will use a latent variable framework analysis to estimate simultaneously the multiple proposed mediators of ROC and ROC+. A series of multiple-mediator models(42) will provide a test of whether ROC and ROC+ lead to greater changes than AC or BWL (SA1) on a proposed set of candidate mediators (‘a’ paths for mid-treatment and post-treatment increases in sensitivity to appetitive cues & reactivity to food cues and inhibitory control over food cues; less dietary restraint, binge eating & overeating) and whether changes in mediators are related to greater change in weight loss (BMI, *%* body fat, binge eating) at the end of treatment (‘b’ paths). The product of these sets of coefficients and associated standard errors will provide effects used to test statistical significance. Evaluation of moderators will add a set of two interaction effects of dummy-coded treatment indicators with demographics, baseline BMI, binge eating status, sensitivity to appetitive cues, reactivity to external food cues, inhibition for LME models evaluating PA1 and PA2. Significance of moderators will be evaluated with an adjustment for multiple tests using Benjamini Hochberg procedures.(43) Participant liking, acceptability, and retention (i.e. attendance) of each treatment will be evaluated with regression models to identify individual characteristics associated with these outcomes.

4.3 Missing data

The maximum-likelihood (ML) based analysis using the observed data from all cases assumes missing data is missing at random (MAR) and the missing data is a function of the observed outcomes and covariates. The plausibility of the MAR assumption with ML can be improved by using an inclusive analysis strategy that incorporates auxiliary variables as correlates of missingness. We acknowledge the possibility that data may be missing not at random (MNAR). Therefore, we propose to perform MNAR sensitivity analyses using pattern mixture models. For infrequently observed patterns we will apply the Hedeker and

Gibbons approach(44) that uses a binary variable in the model to denote missing data at one or more time points.

5. Discussion

The PACIFIC study is an ongoing fully-powered randomized controlled trial comparing our novel treatment, ROC, as a stand-alone treatment and in combination with BWL, with BWL and an AC group among adults with overweight and obesity over 24-months. The PACIFIC study will provide integral knowledge of whether the ROC program and the combined ROC + program provide greater decreases in weight (BMI, %weight lost, body fat %) and decreased binge eating as compared to BWL and AC. Importantly, this study will also evaluate changes in key hypothesized mechanisms of action, including sensitivity to appetitive cues, reactivity to external food cues, inhibitory control when exposed to food cues, dietary restraint, energy intake and overeating. We will also determine whether the three intervention arms (ROC, ROC+, BWL) promoted increased physical activity relative to AC. We will explore potential mediators (e.g., sensitivity to appetitive cues, reactivity to food cues, inhibitory control over food, dietary restraint & overeating) as well as moderators (e.g., demographics, baseline BMI, binge eating status, sensitivity to appetitive cues, reactivity to external food cues, inhibitory control over food) of treatment outcomes (BMI, % body fat, binge eating). Further analysis of PACIFIC data will allow us to evaluate attrition, adherence and attendance patterns throughout treatment.

The PACIFIC study was designed to evaluate a novel treatment, ROC, as a stand-alone treatment and in combination with BWL, to improve weight loss and weight loss maintenance, as well as to target binge eating. By targeting underlying mechanisms, such as sensitivity to hunger and satiety cues, external food cue responsiveness, and inhibitory control, we hope to inoculate participants against the ubiquitous food cues in the current environment. The PACIFIC data set will include a wide array of appetitive traits, which could be used to identify behavioral phenotypes and responsiveness to the different treatments, which could lead to precision medicine approaches.

PACIFIC is a tightly controlled trial with one year of treatment and one year of follow-up. By controlling enrollment, we will be able to directly compare the three active treatments with the AC with less variability in sample characteristics. The design of the study will allow us to test ROC as a stand-alone treatment as well as a combined version with BWL resulting in a cost-effective way to evaluate all the different treatments at once in one study. As in all studies, the PACIFIC study has limitations. First, it was conducted in a University clinic with well-trained staff, and the treatments may not translate directly to community-based clinics. Additionally, the demographics of the PACIFIC study are unique (20% Hispanic) and may not generalize directly to other racial/ethnic groups (e.g., African Americans and Asians). Relatedly, although rates of overweight/obesity across men and women are similar (45), the current sample is predominantly female; however, this is common in many weight loss trials. (46–48) Despite these limitations, the PACIFIC study will be the first to compare the ROC and ROC+ models with BWL and AC with a 12-month follow-up and provide data on appetitive mechanisms and the relationship to weight loss over time.

Acknowledgements

We would like to acknowledge all the participants as well as the staff at CHEAR, without whom this study would not be possible.

Funding:

This work was supported by the National Institutes of Health [R01DK103554, K23DK114480, UL1TR001442]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Diabetes Prevention Program (DPP) Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care. 2002; 25(12):2165–71. [PubMed: 12453955]
2. Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with Type 2 diabetes: One-year results of the Look AHEAD trial. Diabetes Care. 2007; 30(6):1374–83. [PubMed: 17363746]
3. Wadden T, Butryn M, Wilson C. Lifestyle modification for the management of obesity. Gastroenterology. 2007; 132(6):2226–38. [PubMed: 17498514]
4. Wadden T, West D, Neiberg R, et al. One-year weight losses in the Look AHEAD study: factors associated with success. Obesity (Silver Springs). 2009; 17(4):713–22.
5. Wing R, Hamman R, Bray G, et al. Achieving weight and activity goals among diabetes prevention program lifestyle participants. Obes Res. 2004; 12(9):1426–34. [PubMed: 15483207]
6. Dombrowski S, Knittle K, Avenell A, Araujo-Soares V, Sniehotta F. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. BMJ. 2014; 348:g2646. [PubMed: 25134100]
7. Carnell S, Benson L, Pryor K, Driggin E. Appetitive traits from infancy to adolescence: using behavioral and neural measures to investigate obesity risk. Physiol Behav. 2013; 121:79–88. [PubMed: 23458627]
8. Llewellyn C, Wardle J. Behavioral susceptibility to obesity: Gene-environment interplay in the development of weight. Physiol Behav. 2015; 152(Pt B):494–501. [PubMed: 26166156]
9. Carnell S, Wardle J. Appetite and adiposity in children: Evidence for a behavioral susceptibility theory of obesity. Am J Clin Nutr. 2008; 88(1):22–9. [PubMed: 18614720]
10. Schachter S Some extraordinary facts about obese humans and rats. Am Psychol. 1971; 26(2):129–44. [PubMed: 5541215]
11. Schachter S, Rodin J. Obese humans and rats. Hillsdale NJ Erlbaum 1974;
12. Boutelle N, Knatz S, Carlson J, Bergmann K, Peterson C. An open trial targeting food cue reactivity and satiety sensitivity in overweight and obese binge eaters. Cogn & Behav Pract. 2017; 24(3):363–73.
13. Boutelle K, Zucker N, Peterson C, Rydell S, Cafri G, Harnack L. Two novel treatments to reduce overeating in overweight children: a randomized controlled trial. J Consult Clin Psychol. 2011; 79(6):759–71. [PubMed: 22122291]
14. Boutelle K, Zucker N, Peterson C, Rydell S, Carlson J, Harnack L. An intervention based on Schachter's externality theory for overweight children: the regulation of cues pilot. J Pediatr Psychol. 2014; 39(4):405–17. [PubMed: 24459240]
15. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropspychiatric Interview (M.I N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998; 59(20):22–33;quiz 4–57.
16. Cooper Z, Fairburn C. The eating disorder examination: semi-structured interview for the asessment of the specific psychopathology of eating disorders. Int J Eat Disord. 1987; 6:1–8.
17. Fairburn C, Cooper Z, O'Connor M. Eating Disorder Examination, Edition 17.0D; April, https://www.credo-oxford.com/7.2.html. 2014.

18. Berg K, Peterson C, Frazier P, Crow S. Psychometric evaluation of the eating disorder examination and eating disorder examination-questionnaire: a systematic review of the literature. Int J Eat Disord. 2012; 45(3):428–38. [PubMed: 21744375]
19. Fairburn C, Beglin S. Eating Disorder Examination Questionnaire (EDE-Q 6.0) Fairburn CG (Ed.), Cognitive behavior therapy and eating disorders. Guilford Press, New York 2008:309–13.
20. Fairburn CG, Beglin S. Assessment of eating disorders: interview or self-report questionnaire? Int J Eat Disord. 1994; 16:363–70. [PubMed: 7866415]
21. Gormally J, Black S, Daston S, Rardin D. The assessment of binge eating severity among obese persons. Addict Behav. 1982; 7(1):47–55. [PubMed: 7080884]
22. Timmerman G Binge Eating Scale: Further assessment of validity and reliability. J Applied Biobehav Res. 1999; 4(1)
23. Tylka T, Kroon Van Diest A. The Intuitive Eating Scale-2: item refinement and psychometric evaluation with college women and men. J Couns Psychol. 2013; 60(1):137–53. [PubMed: 23356469]
24. Lowe M, Butryn M, Didie E, et al. The Power of Food Scale. A new measure of the psychological influence of the food environment. Appetite. 2009; 53(1):114–8. [PubMed: 19500623]
25. Espel-Huynh H, Muratore A, Lowe M. A narrative review of the construct of hedonic hunger and its measurement by the Power of Food Scale. Obes Sci & Pract. 2018:1–12.
26. Nederkoorn C, Smulders F, Jansen A. Cephalic phase responses, craving and food intake in normal subjects. Appetite. 2000; 35(1):45–55. [PubMed: 10896760]
27. Malik M, Camm A, Bigger J, et al. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. European Heart J. 1996; 17(3):354–81. [PubMed: 8737210]
28. Logan G On the ability to inhibit thought and action: A user's guide to the stop signal paradigm In: Dagenbach D, Carr TH, (eds). Inhibitory processes in attention, memory, and language. San Diego: Academic Press 1994:189–239.
29. Logan G, Cowan W. On the ability to inhibit thought and action: A theory of an act of control. Psychological Review. 1984; 91:295–327.
30. Stunkard A, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. J Psychosom Res. 1985; 29(1):71–83. [PubMed: 3981480]
31. Allison D, Kalinsky L, Gorman B. A comparison of the psychometric properties of three measures of dietary restraint. Psychol Assess. 1992; 4(3):391–8.
32. Diet History Questionnaire. Version 2.0. National Institutes of Health, Epidemiology and Genomics Research Program, National Cancer Institute. 2010 2010;
33. Diet*Calc Analysis Program. Version 1.5.0. National Cancer Institute, Epidemiology and Genomics Research Program. 10 2012;
34. DHQ Nutrient Database. dhq2.database.092914.csv. National Cancer Institute, Epidemiology and Genomics Research Program;
35. Tanofsky-Kraff M, Ranzenhofer L, Yanovski S, et al. Psychometric properties of a new questionnaire to assess eating in the absence of hunger in children and adolescents. Appetite. 2008; 51(1):148–55. [PubMed: 18342988]
36. Blair S, Haskell W, Ho P, et al. Assessment of habitual physical activity by a seven-day recall in a community survey and controlled experiments. Am J Epidemiol. 1985; 122(5):794–804. [PubMed: 3876763]
37. Gross L, Sallis J, Buono M, Roby J, Nelson J. Reliability of interviewers using the Seven-Day Physical Activity Recall. Res Q Exerc Sport. 1990; 61(4):321–5. [PubMed: 2132889]
38. Dunn A, Marcus B, Kampert J, Garcia M, Kohn Hr, Blair S. Comparison of lifestyle and structured interventions to increase physical activity and cardiorespiratory fitness: a randomized trial. JAMA. 1999; 281(14):327–34. [PubMed: 9929085]
39. Godin G, Shephard R. A simple method to assess exercise behavior in the community. Can J Appl Sport Sci. 1985; 10(3):141–6. [PubMed: 4053261]
40. Jacobs DR, Ainsworth BE, Hartman T, Leon A. A simultaneous evaluation of ten commonly used physical activity questionnaires. Med & Sci in Sports & Exercise. 1993; 25:81–91.

41. Fritz M, Mackinnon D. Required sample size to detect the mediated effect. Psychol Sci. 2007; 18(3):233–9. [PubMed: 17444920]

42. Preacher K, Hayes A. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods. 2008; 40(3):879–91. [PubMed: 18697684]

43. Benjamini Y, Hochberg Y Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Royal Statist Soc B-Methodological. 1995; 57(289–300)

44. Gibbons R, Hedeker D. Random effects probit and logistic regression models for three-level data. Biometrics. 1997; 53(4):1527–37. [PubMed: 9423267]

45. Fryar C, Carroll M, Ogden C. Prevalence of overweight, obesity, and severe obesity among children and adolescents aged 2 – 19 years: United States, 1963 – 1965 through 2015 – 2016. National Center for Health Statistics Health E-Stats. 2018;

46. Smith S, Weissman N, Anderson C, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. New Engl J Med. 2010; 363(3):245–56. [PubMed: 20647200]

47. Burke L, Styn M, Sereika S, et al. Using mHealth technology to enhance self-monitoring for weight loss: a randomized trial. Am J Prev Med. 2012; 43(1):20–6. [PubMed: 22704741]

48. Jakicic J, Davis K, Rogers R, et al. Effect of wearable technology combined with a lifestyle intervention on long-term weight loss: The IDEA Randomized Clinical Trial. JAMA. 2016; 316(11):1161–71. [PubMed: 27654602]

Table 1.

Measurement table and assessment time points.

		Time-point					
	Instrument (references)	**1**	**Trt visits**	**2**	**3**	**4**	**5**
Demographics	Age, gender, ethnicity, income	X					
	Barratt Simplified Measure of Social Status	X					
Anthropometry	Height and Weight (BMI)	X	X	X	X	X	X
	Body composition (DXA)	X			X		X
Medical and Psychiatric History	MINI	X					
	Medical history questions	X	X	X	X	X	X
Binge Eating	Eating Disorder Examination	X		X	X	X	X
	Eating Disorder Examination Questionnaire	X	X	X	X	X	X
	Binge Eating Scale	X	X		X		X
Sensitivity to appetitive cues	Intuitive Eating Scale	X	X	X	X	X	X
Reactivity to external food cues	Psychophysiological measurements	X			X		X
	Power of Food Scale	X	X	X	X	X	X
Inhibitory control in response to food cues	Stop Task with food pictures	X		X	X	X	X
Energy intake	Dietary History Questionnaire – II (DHQ-II)	X		X	X		X
Overeating	Eating in the Absence of Hunger Questionnaire	X		X	X	X	X
Dietary restraint	Three Factor Eating Questionnaire (Restraint)	X	X	X	X	X	X
Physical activity	Physical Activity Recall	X	X	X	X	X	X
	GODIN Leisure-time exercise questionnaire	X	X	X	X	X	X

Note: Timepoints were as follows 1 = baseline, Trt visits = treatment visits (26 sessions over 12 months), 2 = mid-treatment (6-months), 3 = post-treatment (12-months), 4 = 6-month follow-up (18-months), 5 = 12-month follow-up (24-months).

Table 2.

Key components and differences between the four arms.

	ROC	BWL	ROC+	AC
Dietary prescription	No dietary prescription. Sessions focused on learning to control physiological and psychological responding to food, and to eat less of foods that are palatable. No education about portion control or food labels.	Restricted calories to 1200 or more based on weight using a low fat, low calorie diet. Sessions included problem-solving barriers to following the diet, learning about food labels, food shopping, cooking and portion control.	Restricted calories to 1200 or more based on weight using a low fat, low calorie diet. Participants learned to control physiological and psychological responding to food, as well as food labels, shopping, cooking and portion control	Healthy eating using choosemyplate.gov. Participants learned about food labels, shopping, cooking and portion control.
Self-monitoring	Hunger and craving	Food intake	Food intake, hunger and craving	None
Experiential learning	Participants brought meals and/or palatable foods to each session. Hunger and satiety was monitored in session during meals Exposures to highly craved foods were conducted in session while cravings were monitored.	None	Participants brought meals and/or palatable foods to each session. Hunger and satiety was monitored in session during meals Exposures to highly craved foods were conducted in session while cravings were monitored.	Mindfulness Activities
Physical activity prescription	Physical activity was prescribed to help regulate physiological and psychological responding to food cues. Actual program is the same as BWL.	Physical activity was prescribed to burn calories to assist in weight loss.	Physical activity was prescribed to burn calories to assist in weight loss, as well as to help regulate responding to food cues. Actual program is the same as BWL.	Physical activity was recommended for health and stress management. Same goal of weekly exercise was recommended.
Stimulus control	Focus was on tolerance and mastery of physiological/ psychological arousal at restaurants and parties. Did not recommend avoiding any eating situations.	Recommended removing palatable energy dense foods from the home, and planning ahead for eating in restaurants and parties, and avoiding high-risk eating situations.	Tolerance and master of physiological and psychological arousal to food cues, removing palatable energy dense foods from the home, and minimizing and preparing for high-risk situations.	None
Goal setting	Goal setting focused on self-monitoring and practicing mastery and toleration of physiological/psychological arousal.	Goal setting focused on self-monitoring, and adherence to diet and physical activity.	Goal setting focused on self-monitoring (food intake, hunger and cravings) and adherence to diet and physical activity	None
Coping skills	Methods for managing psychological and physiological arousal. Discussed each week regarding mastery and tolerance of physiological/ psychological arousal.	Discussed in terms of how to cope to reduce barriers to diet and physical activity adherence	Methods for managing psychological and physiological arousal. Discussed each week regarding mastery and tolerance of physiological/psychological arousal.	None
Other health issues	None	None	None	Sleep, stress