Protocol Title: 24 Week External Single-arm Study Testing the Effectiveness of WW GLP-1 behavioral program + Sequence medical weight management on Weight Loss and Related Outcomes

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Sponsor: WW International, Inc.

1. Overview

Objective: To evaluate the efficacy of the WeightWatchers (WW) GLP-1 behavioral program + Sequence medical weight management program on weight loss and related outcomes.

Design: This is a 24 week prospective single-arm efficacy outcomes study.

Participants: Up to 180 adult participants who are currently enrolled in WW GLP-1 behavioral program program + Sequence medical weight management program and already prescribed semaglutide or tirzepatide.

Primary Aim: Effect of WW GLP-1 behavioral program + Sequence on weight loss at 24 weeks.

Secondary Aim: Effect of WW + Sequence on weight loss at 12 weeks and % reaching 5, 10, 15, 20 % body weight loss, blood pressure, QOL, well-being, physical activity, diet quality, hunger, stress, internalized weight bias, emotional eating, satisfaction, community at 12 and 24 weeks.

Exploratory Aim: Effect of WW + Sequence on habit strength, food cravings, self-compassion, disordered eating behaviors, side effects, restraint/disinhibition, body appreciation, depression symptoms at 12 and 24 weeks.

2. Background and Rationale with Specific Aims: Obesity is a major public health crisis. The prevalence has been rising steadily among adults, adolescents, and children throughout the world.[1,2] In the United States, 42.4% of adults have obesity (BMI >30 kg/m^2) and approximately 9.2% have Class 3 obesity (BMI >40 kg/m^2).[1] The prevalence of obesity has increased from 30.5% in 2000 to 42.4% in 2018, with Class 3 obesity jumping from 4.7% to 9.2%. The prevalence remains unacceptably high, particularly among some minority populations and pediatric patients.

The effects of obesity on physical, psychological, and economic health are substantial. Obesity is associated with increases in comorbidities, especially type 2 diabetes mellitus and cardiovascular disease. Obesity is also associated with increased hyperlipidemia, hypertension, metabolic syndrome, stroke, asthma, sleep apnea, liver and gallbladder disease, depression, low back pain, urinary incontinence, and several forms of cancer (e.g., breast, prostate, and colon). Individuals with obesity have a 50% to 100% increased risk of death from all causes when compared with individuals in a normal BMI range.[3]

The importance of weight loss in reducing obesity-related morbidity and mortality is well known, but the incidence remains unacceptably high. For patients whose obesity cannot be controlled through lifestyle measures, pharmaceutical treatments are an option. Recent advances in anti-obesity medications (AOM's) have allowed for additional, efficacious treatment options.

Semaglutide was FDA-approved in June 2021 for chronic weight management in adults with overweight or obesity. It is a glucagon-like peptide-1 (GLP-1) hormone that targets receptors for endogenous peptides involved in appetite control. Approval was based on clinical trial results showing significantly more patients in the semaglutide group having clinically important weight loss.[4-5] Adverse events were mostly gastrointestinal, related principally to the class of agent. It requires once weekly subcutaneous injection.[4]

Tirzepatide was FDA approved in November 2023 for chronic weight management in adults with overweight or obesity. Like, semaglutide, tirzepatide is a once-weekly subcutaneous injectable peptide. It is engineered from the native GIP sequence, with agonist activity at both the GIP and GLP-1 receptors[5]. Weight loss has been shown to be highly significant (15-20% of total weight) and like semaglutide, adverse events are primarily gastrointestinal. Both the observed short- and long-term weight loss efficacy for patients with obesity for both tirzepatide and semaglutide necessitate the need for research on this drug class to optimize outcomes.[6]

Clinical trial evidence indicates that lifestyle, diet, and exercise programs that focus on weight loss are effective in the treatment of obesity. If properly implemented, these primary prevention programs can have a significant impact on obesity. Guidelines from the ADA[7] and the AACE/ACE[8] both emphasize the importance of a treatment approach that incorporates lifestyle options. They recommend weight loss in all patients with overweight or obesity to reduce health risks associated with obesity. A 2019 meta-analysis found that behavioral and cognitive interventions that promote reduced energy intake and increased energy expenditure, along with monitoring of this balance, are key factors in weight loss maintenance programs.[9]

The WW Unlimited Workshops and Digital Program is an evidence-based behavioral weight management program[10-15] that guides members toward their weight and wellness goals through a weekly curriculum that is complemented with specific behavioral goals each week across four main pillars (food, activity, sleep, mindset), to drive healthy habits. The WW program is based on recommendations by national and international guidelines to form the foundation for a healthy pattern of eating.[16-17] The WW program includes ZeroPoint™ Foods (a list of foods that can be eaten in moderation without tracking), as well as the proven and proprietary Points system, where foods and beverages are assigned a points value based on their caloric and nutritional content (protein, fiber, unsaturated fat, saturated fat, and added sugar). Using a member's age, height, weight, and sex, a daily points value is calculated, as well as a weekly points target, and members are encouraged to track their food and beverages, with the goal of staying within their daily and weekly points target. Furthermore, the WW Unlimited Workshops + Digital Program offers a community-based approach, providing members with a personalized weight and wellness plan, a weekly check-in and progress report, and coach-led virtual or in-person Workshops that deliver weekly behavior change techniques. In addition, members have access to food, activity, water, sleep, and weight trackers, meal planning tools, recipes and a food barcode scanner, guided meditations and workouts, and always-on support from peers via Connect (a members-only social community) and WW-trained behavior change experts via 24/7 chat with a Coach.

With over 160 published studies, including 38 from randomized controlled trials, WW leads as being the most studied of all commercial behavioral weight management programs. With proven efficacy for weight loss,[10-11] as well as improvements in diet quality[12] and physical and psychological health,[9] WW is at least 2x more effective than do-it-yourself approaches,[13] advice from physicians,[14] and other professionally delivered programs.[15] WW is an accessible and cost-effective weight loss treatment[18-19] and has been shown to be effective for weight loss and glycemic control among those with prediabetes[20] and diabetes.[21] The WW program has now been tailored for individuals taking GLP-1s to provide support for reaching goals that may be important when taking these medications, including adequate protein, fiber, and hydration. Thus, the goal of this trial is to evaluate the efficacy of the new GLP-1 behavioral program.

The application of a comprehensive lifestyle-based intervention focused on dietary intake, physical activity, support and behavioral principles in conjunction with AOM is novel and may increase AOM efficacy while minimizing maintenance concerns. As obesity care can now be delivered virtually, it will also include an innovative strategy of virtual/remotely delivered medical care via Sequence and WW. Further, this study will examine multiple psychosocial domains associated with weight loss and weight

loss related outcomes including physical activity, dietary behavior, disordered eating, depression symptoms, internalized weight bias and community, that have not been examined in AOM trials.

The aims and objectives are as follow:

Aim: To examine the efficacy of WW GLP-1 behavioral program + Sequence for medical weight management for adults with overweight/obesity taking semaglutide or tirzepatide on weight loss and related outcomes

1. Primary Objective: Effect of WW + Sequence on weight loss at 24weeks.
2. Secondary Objectives: Effect of WW + Sequence on weight loss at 12 weeks and % reaching 5, 10, 15, 20% body weight loss, blood pressure, QOL, well-being, physical activity, diet quality, hunger, stress, internalized weight bias, emotional eating, satisfaction, community at 12 and 24 weeks.
3. Exploratory Objectives: Effect of WW + Sequence on habit strength, food cravings, self-compassion, disordered eating behaviors, side effects, restraint/disinhibition, body appreciation, depression symptoms at 12 and 24 weeks.

3. Study Design

3.1 Patient Population

The study population will consist of patients who are already enrolled in the Sequence and prescribed GLP-1 medications.

3.2 Eligibility Criteria:

Prior to being approached for the study, Sequence medical provider will ensure patients are appropriate for GLP-1 medication treatment. Once patient has been evaluated for and accepted into the medical weight management program, they will be asked if they are interested in the study. Study team does not determine eligibility for medication treatment (i.e., only those already approved for medication will be eligible for enrollment). However, the participant will confirm the items below prior to enrollment into the study:

Inclusion criteria:

1. 18 years or older
2. BMI of ≥30 or BMI of ≥27 with one or more weight related medically qualifying condition (hypertension, dyslipidemia, sleep apnea, cardiovascular disease)
3. Access to a smartphone or tablet that runs iOS/iPadOS 15.0 or later, or Android 7.0 or later
4. A prescription for Wegovy, Mounjaro, or Zepbound

Exclusion criteria:

1. Diabetes
2. Personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia type 2
3. History of pancreatitis within 180 days
4. Previous surgical obesity treatment
5. Use of other anti-obesity medication in last 90 days
6. Use of GLP-1 within the last 180 days

7. Lost weight >11 lbs in the last 90 days
8. Pregnant, breastfeeding, intends to become pregnant, of child-bearing potential and not using a highly effective contraceptive method

3.3 Recruitment Plan

This is a survey study and participants will be referred from Sequence. Sequence providers will determine clinically appropriate candidates for GLP-1 medications semaglutide and tirzepatide. Once approved, patients will be offered the opportunity to take part in this study and they will be directed to a link by Sequence that brings them to the study REDCap site where they will input contact information and answer select prescreening questions. These prescreen questions will be the inclusion/exclusion eligibility items. If all eligibility criteria is met, they will be directed to the eConsent page.

3.4 Consent Process

Participants will be eConsented through CC REDCap. The eConsent will include the modified consent form with a comprehension question to be electronically signed. Fields will include participant's first and last name, version of the consent, date of consent and force a signature field. When the participant completes the survey, they will be taken to a new page where the information they just completed is displayed in an inline PDF in the browser. They will be required to review and certify the information before they can submit the survey. Participants can download a copy of the consent from the inline PDF, and a copy of the certified PDF will be stored in the file repository for the study team. It will be emphasized that this study is completely voluntary and that it will not affect their care with the Sequence medical weight management care team if they chose not to participate.

3.5 Study Procedures

Research does not present greater than minimal risk. This research study is the collection of survey responses, blood pressure and weight readings. Patients will be participating in the WW + Sequence program independent of this evaluative study. All surveys will be completed digitally aatients are not required to be in the local Cleveland area as they are referred from the Sequence team, who conducts telehealth medical weight management across the United States. Participants will not be registered as CC patients and will not be entered in Epic. Study surveys that include CORE measures (see 3.6) will be completed electronically in REDCap. WW will facilitate the collection of dietary quality data via Diet ID, with whom they hold a license with. That information will be added to the REDCap database to be used for analysis. Participants will be enrolled once they have worked with their Sequence provider and acquired their GLP-1 medication. Study coordinator will arrange blood pressure monitor with Bluetooth technology to be mailed to participants home via Withings. Files from the blood pressure monitor will be uploaded as attachments into the REDCap for analysis, or manually entered by participants. WW will mail a scale with Bluetooth technology for reporting weight outcomes. Participants will have access to WW's GLP-1 behavioral program and instructed to sign up for one of the weekly virtual workshop offerings. Passively collected participant data from WW and Sequence platforms will provide insights on workshop attendance and engagement with program offerings. CC, WW, Sequence and Withings will be sending information regarding outcomes, participation, and necessary demographic information to facilitate shipping blood pressure monitor and scale through secure Cleveland Clinic's secure email platform. Participants will receive the survey to their email seven days before the target completion date. If they have not completed it by the target date, they will receive an email reminder to complete the survey. The visit window will be -7 days to + 7 days of target date. Participants will be able to complete the study visit outside of the window. It will not be considered a deviation if surveys are completed outside of a window or not at all. Participants will be emailed a link every 4 weeks to complete their medication adherence questionnaire for a more accurate recall period.

PHI will be collected as part of the study and may be shared with the study sponsor as outlined in the consent form for purposes related to this study. Aggregate data will be coded with direct identifiers (such as name and date of birth) removed. Results will be reported in aggregate with no identifiers.

3.6 CORE Measures – Assessed at 0, 12 weeks & 24 weeks

1. Demographics:
   Age, Sex assigned at birth, Gender identity, Martial status, Education, Ethnicity, Race, Household composition, Household Income, Subjective Social Status
2. Behavioral:
   Physical Activity and Sedentary Behavior (Global Physical Activity Questionnaire, GPAQ), Habit Strength (Self-reported behavioral automaticity index, SRBAI), Stage of Change for Strength Training, Strength Training Behavior
3. Psychosocial:
   Food Cravings (Food Cravings Inventory, FCI-II), Hunger (Hunger VAS), Quality of Life (Impact of Weight on Quality of Life- Lite, IWQOL-Lite), Self-Compassion (Self-Compassion Scale), Well-Being (WHO Well-Being Index 5, WHO-5), Perceived Stress (Perceived Stress Scale, PSS-10), Weight Bias (Weight Bias Internalization Scale, WBIS-2F), Emotional Eating (Palatable Eating Motives Scale- Coping Subscale, PEMS-coping), Eating Disorders (Eating Disorder Examination-Questionnaire, EDE-Q), Restraint/Disinhibition (Three Factor Eating Questionnaire- TFEQ), Body Appreciation (Body Appreciation Scale, BAS-2), Loss of Control Eating, LOCES-brief), Depression Symptoms (Patient Health Questionnaire-8, PHQ-8), Patient Reported Outcomes Measurement Information Scale (PROMIS) Applied Cognition-Abilities scale
4. Environmental:
   Food Availability (MESA Neighborhood Healthy Food Availability)
5. WW:
   Community Mechanisms, Satisfaction Survey
6. Clinical:
   Weight, Blood pressure
7. Other:
   Medication Adherence

4. Participant Compensation

Participants will be compensated $40 for each visit completed for a total of $120 ($40 x 3 visits). Participants will be paid via check request. They will be providing full name, DOB, SSN and address to process payment. They can also choose to participate without receiving a stipend. Participants who are enrolled in this study will have their Sequence and WW monthly membership fees waived for the 24 week duration of the study.

5. Risks/Benefits of Research

This is a minimal risk study. We will assume all safeguards to reduce risk of loss of identifiable data. Possible loss of confidentiality could occur. All research and clinical data collected at each study timepoint will be collected directly into REDCap database. Diet ID and participant engagement data will be transferred via Cleveland Clinic secure email platform and incorporated into the the REDCap database.

There are no direct benefits for individuals participating in this study. The knowledge to be gained from this research may benefit other patients, society, and science.

6. Statistical Analysis and Data management/Data Collection

6.1. Determination of Sample Size

The proposed sample size of 180 patients is determined based on a reasonable number of subjects for study participation to provide a representative assessment of program performance, rather than specific statistical hypothesis of study endpoints.

6.2. Statistical Methods

All descriptive statistical analyses will be performed using R, unless otherwise noted. Data will be captured from patient and provider completed surveys and study devices. All data will be stored in REDCap, where it will then be exported for analysis. Derived variables will be programmed by the study programmer/statistician.

6.2.1. *Demographics and Other Patient Characteristics*

Baseline demographic and clinical characteristics will be summarized by descriptive statistics. A tabulation of subject characteristics will be provided including the number enrolled, the number of patients who received each AOM medication, number of patients with available data of the primary endpoint, and the number of withdrawals, including reasons for withdrawal as documented on the CRF.

6.2.2. *Primary and Secondary Endpoint Analysis*

Due to the single-arm study design, all primary and secondary endpoints will be evaluated using descriptive statistics only. No hypothesis tests will be performed.

All baseline and changes in core measures will be evaluated. Statistics for continuous measures will include N, mean, median, standard deviation, minimum, and maximum. Binary measures will be summarized using frequencies and percentages with 95% confidence intervals. For categorical measures, the number and percentage within each category of the parameter will be calculated.

6.2.3. *Subgroup Analysis*

The primary and secondary measures will be evaluated based on specific demographic and clinical subgroups (e.g., sex, BMI class). Comparisons between subgroups will be performed using Student t-tests for continuous variables and proportion tests for binary variables. All results will be adjusted for multiple testing using the Benjamini Hochberg false discover rate (FDR) approach[22]. An FDR $P <$. 10 will be used as the threshold for statistical significance.

6.2.4. *Adjustments to Confounding Factors*

We will be performing an intent-to-treat analysis. No adjustment for covariates will be made; however, subgroup analysis will be performed to determine if significant differences between key subgroups are observed.

6.2.5. *Handling of Dropouts or Missing Data*

We will be performing an intent-to-treat analysis. Only enrolled subject data that are collected will be included in the analysis. All efforts will be made to reduce missing data. In general, missing data will not

be imputed in this study. Where imputation is deemed appropriate, mean, multiple, or last observation carried forward imputation will be considered.

7. Safety Monitoring

Adverse events and side effects related to study drug will be monitored by the Sequence provider monthly during clinical care visits. Participants will be told to inform their PCP provider of any other adverse events or side effects unrelated to AOM occurring during study participation.

Patients will be completing the Patient Health Questionnaire (8 depression screening questions, excluding suicidality). If their score is ≥10, patients will receive a pop up within REDCap letting them know they may be experiencing depression. The pop-up warning will tell them to check in with the primary care doctor about their mood symptoms and will also provide a warning for them to call 9-1-1 if their symptoms get worse or to go to their nearest ED. It will also provide a phone number for the crisis hotline. Patients will be taking their blood pressure using the blood pressure monitor sent to them. The readings will be collected within the Withings app as well as on the device. Patients will either upload the data file into their participant record in REDCap or will manually enter their readings into the REDCap survey at the designated visit. The Withings blood pressure monitor alerts the patient if their reading is high (with instructions to contact their primary care provider). Included with the blood pressure monitor is instructions for best practice for taking blood pressure as well as information within the Withings app. This study will not be collecting any adverse events related to high blood pressure or high PHQ-8 scores.

8. Clinicaltrials.gov

This study will be registered on clinicaltrials.gov.

9. References

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