Impact of Augmented Care at the Worksite for Diabetes Prevention

Study Protocol and Analytic Plan

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1.0 Introduction

The purpose of this document is to provide guidelines regarding study procedures for the Impact of Augmented Care at the Worksite for Diabetes Prevention trial. This trial is a single-site clinical trial. Funding for the trial is provided by the National Institute for Diabetes and Digestive and Kidney Diseases at the National Institutes of Health. Since the trial is funded by the federal government, we are responsible for following federal guidelines and completing federal reports.

2.0 Brief Overview of the Study Protocol

The purpose of this study is to implement and evaluate a lifestyle intervention for Ohio State University (OSU) employees with prediabetes to determine the impact of the intervention on weight loss and related outcomes to reduce risk for type 2 diabetes mellitus (T2DM). People with prediabetes are at high risk for progressing to T2DM, and weight loss is the most effective treatment for risk reduction. This study trial follows a preliminary trial to evaluate the efficacy of a lifestyle intervention implemented at a university worksite. The efficacy trial was highly successful in promoting weight loss on average among participants randomized to the experimental group. However, about 50% of experimental participants did not achieve clinically meaningful weight loss. More effective treatments are needed for people who are slower to respond to behavioral interventions. A goal of this trial is to determine whether augmented care for slow responders promotes greater weight loss and risk reduction. Effective weight loss maintenance interventions also are needed to reduce risk for T2DM. We will examine the impact of an extended intervention phase on weight loss maintenance following an intensive lifestyle intervention.

The specific aims of this translational study at a university worksite are to:

Specific Aim 1: Implement the first 4-sessions of the core 16-session phase of the Group Lifestyle Balance (GLB) intervention for diabetes prevention to all study participants. GLB is the group-based version of the intervention implemented in the Diabetes Prevention Program. Determine percent weight change at week 5. Provide a 12-session augmented intervention (called Group Lifestyle Balance Plus (GLB+)) to participants who fail to achieve > 2.5% weight loss at week 5; provide the remainder of the 12-session standard GLB intervention to all other participants. GLB+ will be enhanced with training in values clarification, mindful decision making, planning, and problem solving. Evaluate the impact of the augmented GLB+ intervention to the standard GLB intervention immediately following the core intervention phase (4 months from baseline).

Specific Aim 2: Create matched pairs of participants based on sex and percent weight change at 4-months following the core intervention phase. Randomly assign each person in the pair to either the standard GLB intervention or to the augmented GLB+ intervention for the 8-month extended intervention phase. Evaluate the impact of the GLB+/GLB+ intervention sequence to the GLB/GLB intervention sequence at 12- and 18-month follow-up. One exploratory sub-aim will be to identify optimal treatment sequences embedded in the adaptive design on percent weight change at 18 months.

Specific Aim 3: Estimate the costs and cost-effectiveness of each intervention from a health system and societal perspective.

3.0 Study Staff Responsibilities

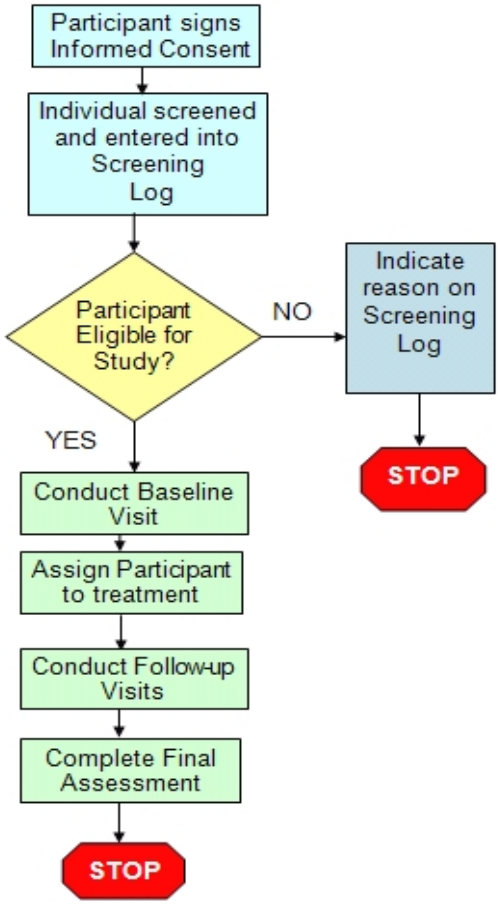
In this single-site study, the site staff perform the following functions:

- Develop all study materials including the Procedures Manual and study forms
- Monitor for and report Adverse Events and Serious Adverse Events
- Obtain informed consent from each participant
- Recruit, screen, and enroll participants
- Randomize participants
- Collect study data and follow participants through study completion
- Comply with study intervention administration
- Protect participants' rights
- Submit documents to regulatory bodies (i.e., IRB, Safety Officer, NIDDK)
- Develop and implement:
    - Data management procedures including the data flow and procedures for data entry, error identification, and correction
    - Quality control procedures
    - Reports - enrollment, participant status (e.g., withdrawals), adverse events, and independent safety monitoring body reports

4.0 Study Flow Diagram

An overview of the general study processes is provided in Figure 1. In this trial, participants are not randomized to treatment group at baseline. Instead, all participants receive the first four weeks of the standard GLB intervention. During these first four weeks, participants learn basic skills such as self-monitoring, the calorie and fat content of food and beverages, and how to initiate a physical activity program such as brisk walking. Participants then remain in the standard GLB intervention if they achieve at least 2.5% weight loss at week 5. If participants do not achieve this level of weight loss, they will be stratified to the augmented GLB+ intervention at week 5. Participants will be randomized to treatment group following the core intervention phase (first 16 weeks) for the extended (8 months) and maintenance (6 months) intervention phases.

Figure 1: Study Flow Diagram



5.0 Recruitment and Retention

A wide variety of recruitment strategies will be used to attract and enroll a sufficient number of participants into the study. A general description of avenues for recruitment and tips for professional engagement are included in the Recruitment Guidelines. Only IRB approved recruitment material can be used. Any changes or additions to recruitment material must be reviewed and approved by the IRB prior to using.

It is vital to not only recruit participants but also retain participants in the study until the final data collection visit, 18 months from baseline. To promote retention, the following procedures will be used:

- Mail birthday cards to participants during their birthday month;
- Mail holiday cards to participants during key holidays (exclusive of religious holidays)
- Provide contact information to participants for the PI, Study Coordinator, and Lifestyle Coach

- Contact participants in the manner they prefer; use e-mail or phone messages based on the participant's preferred method of communication
- Schedule clinic visits and study appointments at a convenient time for the participant
- Reschedule missed appointments as soon as possible
- Provide a parking voucher for participants for study visits who do not have a valid OSU parking permit
- Provide a modest honorarium for completing data collection visits

Use blue ink when signing greeting cards. Use professional language and sentiments in all communications. Letters and other correspondence should be placed on study letterhead.

5.1 Screening and Eligibility Criteria

OSU is among the largest public universities in the U.S. and employs ~44,000 individuals. Recruitment will include advertisements on the daily electronic news service sent to all OSU employees, notices on campus web sites, information about the study at employee biometric screenings, and through university flyers placed throughout campus. In addition, an email message regarding the study and eligibility criteria will be sent to all university employees. A telephone number and e-mail address will be provided for employees to contact for more information. Those who inquire about the study will receive a description of the study and time commitment and, if interested, complete a telephone screening questionnaire to assess potential study eligibility after providing verbal consent. All potentially eligible employees will be scheduled for an individual appointment to obtain informed consent, complete weight and glucose screenings, and complete the Physical Activity Readiness Questionnaire, Patient Health Quiestionnaire-8, and Binge Eating Scale (see exclusion criteria). Eligible enrollees then will complete baseline data collection, which includes completion of study questionnaires, a food frequency questionnaire, 7-day assessment of physical activity, and assessment of blood lipids and blood pressure.

5.2 Screening Log

The Screening, Enrollment, and Randomization Log will provide documentation of all individuals evaluated for study eligibility. Enter codes documenting the reason for individuals who are ineligible or eligible but decline study participation.

5.3 Eligibility Criteria

5.3.a Inclusion Criteria

The eligibility criteria target a sample at risk for diabetes representative of working adults. Both men and women ≥ 21 years old from all racial/ethnic groups will be eligible. Benefits-eligible employees will need to be employed by OSU through the length of follow-up and commit to attend treatment and assessment appointments. The inclusion criteria represent benefit-eligible employees at OSU, which is appropriate for a working population.

In addition to the above criteria, the goal of the study is to recruit participants with prediabetes. OSU employees are encouraged to complete an annual biometric screening, which includes an A1c assessment. A fasting glucose and A1c measurement will be used in this study to predict risk for impaired glucose tolerance. Height and weight measurement and a blood sample by finger stick will be completed to assess casual capillary blood glucose (CCBG) concentration and A1c for people with a BMI > 24 kg/m^2 (> 21 kg/m^2 for Asians). People with a CCGB ≥ 200 mg/dL will be ineligible and informed that they are at high risk for diabetes and should see their physician to undergo formal testing and follow-up. Individuals with a fasting CCBG of 100-125 mg/dL (110-199 mg/dL if non-fasting in previous 2 hr.) will be potentially eligible. Those with an A1c value of 5.7-6.4% will be potentially eligible. These individuals will be assessed for any exclusionary criteria to determine final study eligibility.

5.3.b Exclusion Criteria

Exclusion criteria include: (a) conditions which would limit the adoption of light/moderate physical activity (PA) such as recent cardiovascular event, severe chronic obstructive pulmonary disease, advanced arthritis, or poorly controlled hypertension; (b) chronic use of medicines known to influence glucose metabolism (i.e., corticosteroids); (c) concurrent participation in a structured weight loss program or counseling for bariatric surgery; (d) pregnant or breast-feeding (the inherent weight fluctuations would limit our ability to interpret their data); (e) score ≥ 10 on the Patient Health Questionnaire-8 indicating moderate to severe depressive symptoms; (f) score ≥ 27 on the Binge Eating Scale indicating a potential eating disorder; (g) unwilling to accept randomization; and (h) planning on moving from the area or changing employment.

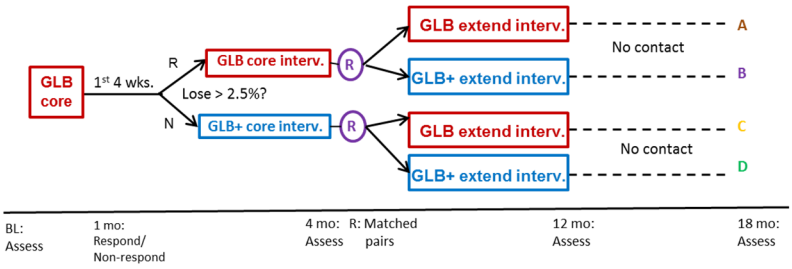
6.0 Informed Consent

Written, informed consent will be obtained once the telephone screening interview has been completed and the individual meets pre-screening eligibility criteria. The Informed Consent form will be mailed to the individual for his/her review prior to the in-person screening appointment. The study Recruitment Coordinator will review study procedures, risks, and benefits verbally with the individual at the in-person screening appointment. The consent form will be reviewed prior to collecting any study data from the individual (e.g., prior to obtaining height, weight, or fingerstick sample). Any questions the person asks will be answered and the individual will be reminded that they do not have to answer any questions they do not want to answer during data collection. The individual and Recruitment Coordinator will sign the consent form in blue ink. The original form will be placed in the participant's study folder and a copy of the form will be given to the individual.

7.0 Research Design and Study Intervention

Following baseline data collection, all participants will begin the 16-session core phase of the Group Lifestyle Balance (GLB) intervention. Percent weight change will be determined at the beginning of week 5, after 1 month of intervention. Those who achieve > 2.5% weight loss will complete the remainder of the 12 GLB sessions. Those who achieve ≤ 2.5% weight loss will be stratified to the Group Lifestyle Balance Plus (GLB+) intervention (additional 12 sessions). A second round of data collection will

occur upon completion of the core intervention study phase, 4 months from baseline. Following this second data collection, participants will be matched into pairs based on gender and percent weight change at 4 months, and each person in a matched pair will be randomly assigned to treatment group for the extended intervention study phase. One person in each pair will receive either the standard GLB intervention or the augmented GLB+ intervention, and the second person in each pair with receive the alternate intervention. Following completion of the extended intervention study phase at 12 months, a third round of data collection will occur. A 6-month no contact phase will follow the extended intervention study phase to evaluate weight loss maintenance. The fourth and final round of data collection will occur upon completion of the 6-month no contact phase, 18 months from baseline.



The goals of both the GLB and GLB+ interventions include losing ≥ 7% of initial body weight and maintaining ≥ 7% weight loss through study end. The intervention group sessions will consist of 10-15 participants (to foster social support) and will be ~ 60 minutes in length held during the noon hour or immediately after work to accommodate participants' work schedules. Those who miss a group session will be encouraged to attend a make-up session prior to the next regularly scheduled session. Approximately 15-20 cohorts of participants will complete the study, and several groups of participants will run concurrently for staffing purposes. Each participant will receive a copy of the weekly printed handouts, a fat and calorie counter, self-monitoring booklets, and a chart for recording body weight. Self-monitoring is a key strategy used during the intervention to promote self-regulation and goal attainment. Participants will be encouraged to self-monitor fat and calorie intake daily, to record their weekly minutes of PA, and to self-weigh (1 day/week in GLB). The monitoring records will be reviewed by the lifestyle coaches weekly with personalized feedback provided to participants.

Following completion of the 16-week core intervention phase, participants will enter the 8-month extended intervention phase. The extended phase will consist of 2 bimonthly group sessions followed by 7 monthly group sessions. The content presented will reinforce skills needed to achieve and maintain the behavioral goals. In addition, we will encourage continued goal attainment through individual goal setting, self-weighing, and social support. Participants will be encouraged to continue to self-monitor periodically (e.g., once/month) and to submit monitoring records for review. Finally, the 6-month maintenance phase of the study that follows the extended intervention phase will include no contact from program staff to assess sustainability of program outcomes.

When a participant does not attend a regularly scheduled group session, a make-up session will be scheduled for that person. The lifestyle coach will contact the participant to determine the reason for the missed session and to remind the individual to attend a

make-up session. Make-up sessions usually will be held immediately prior to the regularly scheduled group session (about 30 minutes in advance). If the participant has a conflict with the schedule for the make-up session, an individual make-up session will be scheduled for that person prior to the next regularly scheduled group session. The participant will be weighed and will be asked to complete the Weekly Check-In Form to assess for adverse events prior to the beginning of the make-up session. Completed self-monitoring records should be turned in as well.

8.0 Randomization

Participants will be randomly assigned to treatment group following the 16-week core intervention phase. Participants will be matched, based on gender and percent weight change following the 4-month data collection visit. Each person in a matched pair will be randomly assigned to either the GLB or the GLB+ intervention for the extended and maintenance intervention phases. The biostatistician will create the randomization log and will be blinded to treatment group during the core intervention phase.

- ***Process Responsibilities***: The Study Coordinator will maintain the master randomization list from the statistician. The Study Coordinator will be responsible for assigning randomization codes, notifying appropriate study staff that the participant has been randomized, and securely storing all randomization files.

The assigned and blinded randomization code, that is separate from study data, will be kept in a paper-based randomization log in a locked filing cabinet.

9.0 Blinding and Unblinding (Masking and Unmasking)

It is not possible to blind study participants to treatment group in an intervention study. The participant, lifestyle coach, study coordinator, and recruitment coordinator are aware of randomization assignment. The participant will be informed to *not* discuss the treatment group to which they were assigned or any specifics of their intervention group with data collectors.

10.0 Safety Reporting

The Check-In Form will be completed by each participant prior to the participant being weighed before the group session begins and at data collection visits. Study staff will note any boxes checked “yes,” indicating a recent illness, injury, hospitalization, or newly prescribed medication. All positive endorsements will prompt completion of the Adverse Event or Serious Adverse Event form. These events may need to be forwarded to the IRB or Safety Officer depending on the seriousness of the occurrence. The Data Safety Monitoring Plan provides a description of adverse events, serious adverse events, and unanticipated events. Please refer to that document for definitions, documents, and reporting procedures. In general, these events will be reported to the PI, IRB, and possibly the Safety Officer as soon as they are identified (no later than 10 days after occurrence per OSU policy).

11.0 Study Compliance

The Study Coordinator maintains the log of all protocol deviations. Deviations will be reported to the PI as soon as they are identified by study staff. Protocol deviations or violations include the following:

- Randomization of an ineligible participant
- Failure to obtain Informed Consent
- Failure to keep IRB approval up to date
- Participant received an incorrect intervention
- Improper procedures used during data collection

The Protocol Deviations Log will be completed for each occurrence and the information will be included in the annual report submitted to the Safety Officer.

The study was registered on the ClinicalTrials.gov website prior to participant enrollment. Guidelines for annual reports will be followed.

12.0 Data Collection and Study Forms

12.1 Participant Folder

All essential study documents will be retained in a participant folder in a locked filing cabinet in the study office. The office will remain locked when staff are not present. The participant folder will be identified by ID number only. Each participant folder will include the following:

- Participant visit schedule form
- Source documents (e.g., fingerstick blood glucose, lipid, and blood pressure results)
- Signed informed consent form
- Questionnaires completed by the participant
- Self-monitoring report forms (and self-monitoring records as needed)
- Pertinent communications with the participant
- Visit checklist forms

12.2 Study Forms

Data collection questionnaires will be administered to participants for study evaluation at baseline, 4-month, 12-month, and 18-month follow-up. The evaluation will enable study investigators to evaluate the impact of the interventions on primary and secondary outcomes. Assessment of psychosocial constructs (e.g., problem solving, goal commitment, motivation), dietary intake, physical activity, metabolic outcomes, and body weight will be obtained. Quality-of-life also will be assessed as a component of the cost effectiveness evaluation. The Schedule of Evaluations indicates when each measure and outcome will be obtained.

12.3 General Instructions for Completing Forms

All data collection forms will include a study ID number and timepoint for data collection at the top of the form. Some forms will include a calendar date as well. These fields will be completed prior to distributing forms to participants. The participant will be informed that all forms do not have to be completed at one time. They will be encouraged to complete the forms across several "sittings," as needed. Items on questionnaires should be completed according to how the participant feels or believes at this moment in time. When the participant returns questionnaires, documents will be reviewed to determine if questions were not answered or skipped. The participant will be asked to answer any inadvertently omitted questions either in person or over the telephone (in person is preferred).

12.4 Data Flow

Data collection staff will review questionnaires when they are returned by participants for completeness and omissions. Participants will be asked to complete skipped portions of questionnaires during the clinic visit. Completed questionnaires will be given to data entry staff for entry into Excel spreadsheets.

12.5 Administrative Forms

Administrative forms will be used to provide documentation of study processes and assist with study operations. Administrative forms include the following:

- Recruitment Contact Log
- Telephone Screening Log
- Screening, Enrollment, and Randomization Log
- Participant Visit Schedule
- Visit Checklist for in-person screening and each clinic visit
- Receipt of Study Honorarium Form
- Participant Self-Monitoring Report Form
- Adverse Event Form
- Serious Adverse Event Form
- Study Deaths Form

12.6 Retention of Study Documentation

All completed paper questionnaires, informed consent forms, outcome measures, and self-monitoring records will be retained. Paper documents will be retained in a locked filing cabinet in a locked office. Only the PI will have a key to this filing cabinet. Electronic records will be retained in a password-protected file on a secure university server.

13.0 Data Management

A data Codebook will be created which includes a code name and numerical value for each variable on each questionnaire and for each anthropometric and clinical outcome. Once data are entered into the appropriate Excel spreadsheet using the proper numerical value, the data will be reviewed for missing, inconsistent, and/or erroneous

entries. At least 25% of all data will be reviewed using the original sources by a second person for data entry errors.

Data quality control checks may identify potential data anomalies such as:

- Missing data or forms
- Out-of-range or erroneous data
- Inconsistent and illogical dates over time
- Data inconsistency across forms and visits
- Not completing all fields of a "completed form" or no reason for missing data is provided

Primarily numerical response categories in data elements will be used to allow for summarization and analysis. A few qualitative responses will be captured (e.g., job title, recruitment sources) for additional summarization. Unnecessary and redundant data elements will be corrected. Original source participant material will be returned to the participant's folder. "Cleaned" data files will be given to the Statistician for data review and analyses.

13.1 External Data

The food frequency questionnaires (FFQ) will be prepared for shipment to NutriQuest for electronic scanning and analyses. The procedures outlined by NutriQuest (Berkeley, CA) for analysis will be followed. The FFQs will be shipped using a tracking procedure. No participant identifiers (e.g., participant name) will be placed on the FFQ other than that requested by NutriQuest. Analyses will include kcal, nutrient values, and portions consumed from food groups.

Physical activity data will be captured via a Fitbit device (San Diego, CA) using software developed by Fitabase (San Diego, CA). An account will be established by study staff to protect participant confidentiality. Each participant will receive a study specific identification number and e-mail address for data monitoring. Step counts and minutes of physical activity will be determined to assess the change in activity levels following intervention implementation.

The Social Problem-Solving Inventory Revised Long Form (SPSI-R:L) will be purchased from Multi-Health Systems (MHS) for administration following a copyright agreement. Information in the header on the SPSI-R:L form will be completed prior to giving to the participant. Provide a number 2 pencil for completing the form. Ask the participant to not tear the form because his/her responses may not transfer through the sheets properly. Only one number should be circled per item. For scoring, separate the QuikScore form. Ensure the responses have transferred through to the scoring grid sheet. Complete the scoring grid by transferring the responses from the left side of the grid to the lightly shaded boxes and the responses from the right side of the grid to the unshaded boxes. Sum the numbers in each column to obtain each scale's raw score. Calculate scores by following the steps on the total raw score derivation sheet. Choose

the appropriate normative sample for the respondent (based on age). Use the total raw score and the scale raw scores for each of the scales to find the standard scores for the person's appropriate age group on the standard score profile sheets.

A copyright agreement will be obtained to administer the Quality of Well Being Self-Administered Scale developed by the Health Services Research Center at the University of California, San Diego. The instrument will be scored according to their scoring guidelines. Similarly, a copyright agreement will be obtained to administer the Euro-Qol-5D-5L instrument from the EuroQolGroup. The instrument will be scored according to their scoring guidelines.

The information needed to conduct the cost-effectiveness analysis will be obtained through a staff-administered questionnaire developed by Dr. William Herman and his research team at the University of Michigan (Ann Arbor, MI). This instrument will be administered at baseline and at the 4-, 12-, and 18-month data collection visits. All data will be de-identified prior to sharing with Dr. Herman's team.

13.2 Quality Control Procedures

All study personnel, including undergraduate assistants, will complete training in the ethical conduct of human subjects' research through the Office of Responsible Research Practice at OSU prior to joining the study. This training will include the CITI training modules, the 9 Good Clinical Practice training modules, and the training modules for the Responsible Conduct of Research. IRB training will be renewed every 3 years. Lifestyle coaches for the intervention also will complete the 2-day training for the Group Lifestyle Balance curriculum led by Dr. David Marrero from the University of Arizona. Training in the GLB+ curriculum for the coaches will be led by Drs. Miller, Cheavens, and Fujita.

At least 20% of the intervention sessions will be randomly selected and audio recorded for intervention fidelity. Participants will provide consent for the recording process. The observer will complete the Intervention Fidelity Checklist, indicating whether the intervention was implemented as planned within 2 weeks of the intervention session. No personally identifying information will be included on the Fidelity checklist. The document will be reviewed by Dr. Miller as soon as it is completed. Departures from the intervention curriculum will be discussed with program staff and additional training will be provided as needed.

13.2.1 Standard Operating Procedures

Standard Operating Procedures (SOPs) will be used to measure height and weight per the National Health and Nutrition Examination Survey anthropometric manual.

Weight Assessment
The following procedures will be used to measure body weight:

- Participants should remove their shoes, coats and heavy jackets, and items from pant pockets (e.g., cell phone, keys, loose change, wallet).
- Direct the individual to stand in the center of the scale platform facing the wall, hands at sides, and looking straight ahead.
- After the person is correctly positioned, obtain the readout on the digital measurement device.
- Ask the person to step off the scale. Allow the scale to reset to zero. Repeat the procedure to obtain a second measurement.

Height Assessment
The following procedures will be used to measure standing height on the stadiometer with a fixed vertical backboard and an adjustable head piece:

- Participants should remove any hair ornaments, buns, or braids from the top of the head.
- Ask the person to stand up straight against the backboard with the body weight evenly distributed and both feet flat on the platform. Stand so that the heels are together and the toes are apart.
- Check that the back of the head, shoulder blades, buttocks, and heals make contact with the backboard. (Some overweight people cannot stand straight while touching all 4 contact points to the backboard. Obtain the measurement with as many contact points as possible.)
- Align the head so that the horizontal line from the ear canal to the lower border of the orbit of the eye is parallel to the floor and perpendicular to the vertical backboard (see diagram on wall). Tilt the head up or down to achieve the proper alignment.
- Lower the stadiometer head piece so that it rests firmly on top of the participant's head with sufficient pressure to compress the hair.
- Instruct the participant to take a deep breath and hold the position.
- Record the height measurement.
- Allow the participant to exhale and relax.
- Repeat the procedure to obtain a second measurement.

Blood Pressure Assessment
Participants will be instructed to avoid smoking, caffeine, or exercise for at least 30 minutes prior to their clinic visit. They should void their bladder prior to taking blood pressure measurements. The following procedures will be used to assess blood pressure:

- Ask the participant to sit all the way to the back of the chair so that the spine is straight.
- Instruct the person to rest quietly for 5 minutes without talking prior to blood pressure measurement.

- Use the right arm for obtaining the blood pressure (BP) measurement unless there is a physical limitation prohibiting use of the right arm (note left arm used on recording form).
- The arm and back should be supported and the legs should be uncrossed with both feet flat on the floor. The arm should be bared and unrestricted by clothing with the palm of the hand turned upward and the elbow slightly flexed. The arm should be positioned so that the midpoint of the upper arm is at the level of the heart. The location of the heart is the junction of the 4th intercostal space and the lower left sternal border.
- Follow the procedures in the manufacturer's technical manual for operating the BP cuff and device.
- Obtain a second BP reading after the person has rested for 30 seconds without talking.

Assessment of glucose, A1c, and lipids will be obtained per procedures outlined in the manufacturer's instruction manuals. Staff will be trained in these SOPs by the manufacturer's training/sales personnel. Participants will be informed to be well hydrated for the fingerstick by drinking water. No other food or beverages should be consumed for at least 8 hours prior to the clinic visit. All records and quality control procedures will be recorded in the laboratory notebook. The refrigerator for phlebotomy supplies and kits will be monitored daily for temperature control. Lancets will be disposed in a sharps container. Disposal of soiled material will be placed in marked containers in the lab and picked up by University services.

14.0 Data and Safety Monitoring Activities

14.1 Study Completion and Close-Out Procedures

Study Completion and close-out procedures will include, but are not limited to, the following:

- Verification that study procedures have been completed, data have been collected, and study intervention and supplies have been returned to the responsible party or prepared for destruction
- Assurance that all data queries have been completed
- Assurance that the investigator will notify the IRB of the study's completion and retain a copy of the notification
- Financial close-out reports
- Preparation of a report summarizing the study's conduct
- Participants will be notified of study completion
- Preparation of peer-reviewed manuscripts for publication

14.1.1 Participant Notification

Dr. Miller and study staff will develop a plan to notify participants that the study is completed, ask participants whether they would like to be informed of the results, and thank them for their participation.

14.1.2 Confidentiality Procedures

Safety measures will be implemented to minimize the risk of breeching confidentiality. Records and forms will be kept in locked filing cabinets when not in use. Computerized data will be accessed only by authorized study personnel and will be password protected. All datasets used for analytic purposes will only contain the participants' study ID number and will not contain personally identifiable information. Study personnel will be educated on the need to maintain confidentiality. All study personnel will complete human subjects training authorized by the OSU Office of Responsible Research Practice. If computers are used to store and/or analyze clinical data, the investigator will address elements of computer security to ensure that the data remain confidential. These elements include but are not limited to: utilization of computer and system passwords, user security training, system testing and verification, and routine system backups to prevent any loss of electronic data.

15.0 Analytic Plan

The data analysis follows a systematic process that begins with checking the data and ends with a rigorous test of specific hypotheses. Descriptive statistics and graphical procedures will be used to examine distributions of the outcomes and transformations of the data will be performed as needed.

15.1 Handling of Missing Data

We routinely follow-up with research participants who do not return instruments during the specified time period, review returned instruments for missing items, and contact people to complete items, if multiple items were skipped to obtain all possible data. The first task is to assess whether the missing data are systematic. We plan to handle the issue of missingness in two steps. We will first compare the proportion of missing values between the two groups and if there is no significant difference, we will assume that the data has the "missing at random" (MAR) structure. We anticipate MAR structure for the repeated measures data. The PROC MIXED procedure in SAS that we will use is capable of producing optimal (maximum likelihood) estimators from the associated likelihoods.

15.2 Specific Aim 1 Analysis

It is hypothesized that there will be no significant difference in percent weight change at four months between treatment groups due to the enhanced training provided to early non-responders. A test of equivalence of the two treatments with percent weight change as the response variable will be performed. A stepwise regression model with

Bayes Information Criterion for choosing the final model will be built. Final test of equivalence will be carried out at level of significance 0.05.

15.3 Specific Aim 2 Analysis

It is hypothesized that participants randomized to GLB+ will on average maintain ≥ 7% weight loss at 12- and 18-months compared to participants randomized to GLB, who are expected to maintain an average loss of 5%. A multiple regression model using the matched pair design described above will be employed in two ways: first, using the percent change at 12- and 18-months as repeated measures nested within matched pairs, and second, as absolute changes using baseline, 12-, and 18-month weights. Significant covariates chosen will be incorporated into these models.

15.4 Specific Aim 3 Cost Effectiveness Analysis

The analysis will be performed with an 18-month within trial time horizon and a longer simulated time horizon. The population considered in the CEA will be participants enrolled in the trial. The main outcome of interest is the incremental cost-effectiveness ratio (ICER) comparing the GLB+ to GLB group estimated by

$$ICER = \frac{Cost(GLB+) - Cost(GLB)}{Effect(GLB+) - Effect(GLB)} = \frac{\Delta Cost}{\Delta Effect}$$

where: the ratio ΔCost/ΔEffect is interpreted as the incremental cost required to achieve one additional unit of health benefit, if the GLB+ extended intervention is used instead of the GLB extended intervention. Analyses will be performed from both a health care and a societal perspective, considering all direct medical and indirect costs as appropriate.

15.4.1 Within-Trial CEA

Utility scores collected in the trial will be combined with cost data to assess the within trial cost-utility of the treatment arms from both a health system (direct medical costs only) and societal perspective (direct and indirect medical costs).

15.4.2 Simulation Modeling CEA

Short-term outcomes (percent change in body weight, change in A1c, change in fasting glucose, etc.) measured for the GLB+ and GLB groups during the trial will be entered into a model derived from data from the DPP to predict progression to diabetes and reversion to normal glucose tolerance at 3 years. These data will then be used to simulate the 5- and 10-year cost-effectiveness of the intervention using the MMD, which allow us to consider all downstream costs including those of the intervention as well as those related to diabetes, its complications, and co-morbidities. All costs will be adjusted to the year 2017 using the U.S. Consumer Price Index. Future costs and health benefits will be discounted by 3% annually. Extensive sensitivity analyses will be conducted to assess the impact of variations in the parameters and assumptions on the outcomes.

Treatment Sequence	Initial Intervention	Subsequent Intervention	Subgroups in Design Figure
1	GLB core	GLB extend	A
2	GLB core	GLB+ extend	B
3	GLB+ core	GLB extend	C
4	GLB+ core	GLB+ extend	D

15.4. Analyses for Comparing Treatment Sequence on Weight Loss Maintenance (sub-aim)

The analysis for this exploratory sub-aim will compare the 4 treatment sequences embedded in the adaptive design on percent weight change at 18-months. The primary comparison of interest is the GLB/GLB intervention sequence to the GLB+/GLB+ intervention sequence across the 18-month timeframe. Whether the GLB+ intervention during the extended intervention phase is optimal following the core phase, especially for early non-responders, and whether the GLB+ intervention during the extended intervention phase is necessary to promote weight loss maintenance for those who initially achieved the 2.5% weight loss will be determined. The analysis will be based on an analysis of covariance model, using appropriate covariates (e.g., baseline weight), where we will compare the four groups using an F-test and then perform multiple comparisons using Tukey's HSD test.