Title: A Pilot Study of a Lifestyle Intervention on the Metabolic Syndrome

NCT02233088

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3.4. Statistical analysis

3.4.1. Preliminary considerations

All statistical analyses will be performed using SAS v. 9.2. Basic summary statistics will be calculated for all outcome variables and covariates of interest. Continuous variables will be checked for normality using Q-Q plots.

3.4.1.1. Missing data. *Analyses will use an intent-to-treat approach that includes all patients randomized. Study procedures have been proposed to minimize loss of data due to withdrawal or loss. However, sensitivity analyses will be employed to assess the impact of missingness and both conservative and liberal imputations will be used.*

3.4.1.2. Adjustment for Clustering*. Clusters exist within the intervention arm and analyses thus require consideration of the effects due to clustering, assessed by analyzing within- and between-cluster variance as well as estimating the intraclass correlation coefficient using generalized linear mixed effects modeling. The cluster effect will be deemed significant if the appropriate covariance parameter estimate obtained from the model has p-value <0.05.*[142] *In this event, rather than using a two-sample, two-sided, z-test to compare proportions between the two treatment arms and the t-test (or the Mann-Whitney test if distributions are sufficiently non-normal) for the comparison of means, the cluster-adjusted chi-square test will be used to compare proportions and the cluster-adjusted t-test (or the cluster-adjusted Wilcoxon Rank-Sum test if distributions are sufficiently non-normal) will be used to compare means. Similarly, rather than using linear regression analysis to analyze relationships between continuous dependent variables and indicated covariates, linear mixed modeling will be employed. Lastly, rather than using logistic regression analysis to assess relationships between dichotomous dependent variables and indicated covariates, generalized linear mixed effects modeling will be employed.*

3.4.2. Data Analysis

Primary Aim 1. *In a randomized design, determine the efficacy of the 12-month ELM Intervention, relative to Education Control, in an ethnically diverse sample of MetS patients. We hypothesize that the ELM intervention will produce a clinically significant remission of the MetS in at least 40% of those treated, while the remission rate in the Enhanced Usual Care Arm will not be higher than 15% at 12 months.*

For each arm, the proportion of patients in remission of MetS at 12 months will be computed. The appropriate 2-sample test (see ‘Adjustment for Clustering’ section) will be used to compare the proportions. We will also test the hypothesis that the intervention produces a 12-month MetS remission rate of ≥40%.

Identification of a clinically significant primary endpoint and threshold on that endpoint is crucial to the determination of whether or not a proposed treatment deserves further testing.[104] *The dichotomous rate of MetS remission (i.e., no longer meeting criteria) is the most popular primary endpoint in clinical trials of the MetS.*[92-94, 105-107] *A continuous MetS score has not been validated in American adults.*[108, 109]

Secondary *Aim 2*. *To assess the sustainability of the combined ELM plus Extended Maintenance Intervention on remission of the MetS at 24 months. We hypothesize that the ELM intervention will produce a clinically significant remission of the MetS in at least 38% of those treated, while the remission rate in the Education Control arm will not be higher than 15%.*

Analytic procedures will be exactly the same as those for the Primary Aim (above).

Secondary Aim 3. *To assess the impact of the 12-month ELM Intervention, and the 24-month ELM plus Extended Maintenance Intervention, on intermediate behavioral outcomes (dietary intake, physical inactivity, and stress) and secondary outcomes (body mass index, vitality, and MetS components).*

Separate analyses will be conducted for each outcome. Mean changes (from baseline to 12 or 24 months) between the two arms will be compared using the appropriate 2-sample test (see ‘Adjustment for Clustering’). The dependent variable will be the respective outcome at 12 or 24 months and the covariate predictors will be the baseline value and treatment allocation.

Exploratory Aim 4. *To develop a system for monitoring costs of the intervention and of medical care over 24 months of follow up in all randomized patients.*

Cost and resource use information will be collected in all patients for the interventions (e.g., time cost for the interventions, productivity loss, enrollment in other wellness programs) and for their health care. Candidate program costs include fixed and variable costs of the ELM Intervention and Education Control. These costs

include the ELM Coach and Coach Assistant time spent delivering the program, time spent training and preparing for each group session and time spent making calls to patients between group sessions, valued at these positions' average hourly wage, group meeting costs (e.g., meeting room space, meals), printed materials, and pedometers. Candidate patient costs include the patient's time spent attending the group sessions, travel time between home and the group sessions, and productivity losses to due absenteeism and presenteeism (measured using the Work Productivity and Activity Impairment Questionnaire),[133] valued at the average wage adjusted for socio-demographic characteristics. Health care and wellness-related costs include the cost of primary care physician visits, emergency department visits, hospitalizations and other health and wellness provider visits.[34] In addition, the cost of participation in other wellness programs will be included, since ELM may be perceived as a substitute for other wellness programs that patients would otherwise engage in. Feasibility and accuracy of all data collected will be determined and a protocol for assessing costs will be developed.

Exploratory Aim 5. *To explore the impact of the ELM intervention at 12 and 24 months on selected biomarkers of CVD (hemoglobin A_{1c}, C-reactive protein, lipoprotein particle composition) and change in the social network.*

Analyses will be approached in the same way as the continuous variables outlined in Secondary Aim 3 above. Change in the social network will focus on: (1) network size; (2) frequency of contacts; and (3) overall social connectedness. We will consider use of analysis of variance with quintiles of social network summary scores[143] to identify network variables are related to MetS remission. In addition, we will specifically assess the number and frequency of contacts with other ELM participants.

Exploratory Aim 6*. To explore the acceptability of the intervention assessed as the screening to enrollment ratio, the dropout rate within each arm, and the perceived credibility of each arm.*

The DMC will keep records of screened, enrolled, and drop-out rates. Mean differences in credibility between the 2 arms will be assessed in the same way as the continuous variables outlined in Secondary Aim 3 above.

Exploratory Aim 7. *To explore the moderating effects of built and food environment on MetS remission in the ELM Intervention and Control arms at 12 and 24 months.*

Moderating effects will be tested using logistic regression analysis (see 'Adjustment for Clustering' section above) with the dependent variable of MetS remission and the covariates of treatment arm, moderator, and the treatment-by-moderator interaction term.

3.4.3. Sample Size and Power

The ***primary outcome*** of the study is remission of MetS from baseline to the 12-month visit. We hypothesize that at least 40% of patients in the Intervention Arm, and no more than 15% in the control arm will achieve remission. This hypothesis is supported by the ELM proof-of-concept study and published data on 12- and 24-month MetS remission rates of 9-14% in both control groups' patients.[93, 95, 106] *The proposed study employs clusters within the treatment arm only. To estimate sample size, adjustments were made for the intra-class correlation coefficient (ICC). Using data from the ELM proof-of-concept study, we conservatively estimate the ICC to be*

A two-sample, two-sided, z-test for proportions will be used to compare the rate of MetS remission between the two treatment arms with an overall significance level of 0.05.

The sample size chosen is 48 patients (16/arm). Required sample sizes were computed under several plausible scenarios, indicated by our proof-of-concept study and other relevant studies. Power was set at 80%, alpha was 0.05, and a 20% dropout rate was assumed. **Figure 5** shows that if a sample size of 48 is chosen, there will be adequate power to detect a statistical difference between a remission rate as low as 40% in ELM Intervention arm and as high as 15% in the Education Control arm. Similar sample sizes resulted when the number of participating sites, clusters per site, and patients per cluster (between 10 and 13) were varied. There will be inadequate power to detect an effect if the ELM Intervention effect erodes to below a 38% remission and the Education Control remission rate is as high as

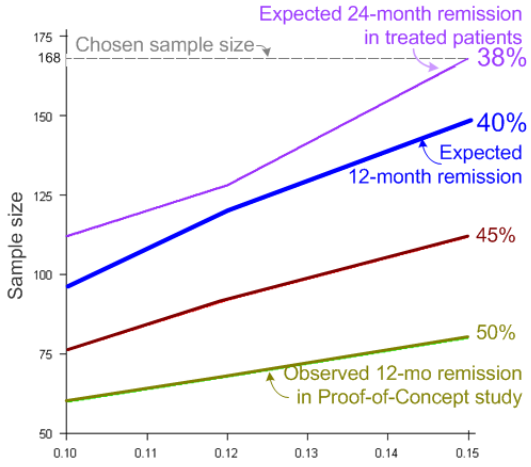

Figure 5. Sample size MetS remission rates of 50, 45, 40, and 38% in the ELM Intervention Arm after 24 months (represented by lines), and 10-15% remission rates in the Education Control Arm.

15%. However, this state of affairs would suggest that more developmental work on either the treatment or control group is needed before progressing.