Supplemental Online Content

Lowe DA, Wu N, Rohdin-Bibby L, et al. Effects of time-restricted eating on weight loss and other metabolic parameters in women and men with overweight and obesity: the TREAT randomized clinical trial. JAMA Intern Med. Published online September 28, 2020. doi:10.1001/jamainternmed.2020.4153

Statistical Analysis Plan – Revision 9/1/19 – Finalized prior to locking the database and prior to any data analysis (except as noted*)

An initial power analysis showed that with a standard deviation (SD) of 9 kg in measured weight, and conservatively assuming a intraclass correlation (ICC) of 0.8 between the baseline and follow-up weights, the clinical sample of 50 participants would provide 80% power in 2-sided 5% tests to detect a between-group difference in weight change of 5.0 kg.

In addition, before the data analysis was undertaken, we estimated the minimum detectable effects in the planned analyses using linear mixed models (LMMs) for daily weights measured at home by the virtual participants, without using the data. Specifically, we estimated that with gradual attrition of 20% of the sample by the end of the trial, 81 of 90 expected daily measurements per patient would on average be available. Then under the original assumption of an SD of 9 kg, and considering ICCs between 0.8 and 0.95, we estimated that a sample of 100 virtual participants would provide 80% power in 2-sided 5% tests to detect between-group differences in weight change of .44 to .89 kg; in the observed sample of 116, corresponding estimates are 0.41 to 0.82 kg. In the clinical data, with single pre- and post-measurements, corresponding estimates under the same assumptions were 2.5 to 5.0 kg.

The primary outcome will be weight, measured daily via iHealth, among virtual participants. To estimate the intention-to-treat effect of treatment assignment, we will use an LMM with fixed effects for treatment assignment, time since baseline (as a continuous variable with range 0-1), and their interaction, and random effects for participant and time, with unstructured covariance matrix. The treatment effect will be estimated by the fixed effect for the treatment by time interaction. In sensitivity analyses, we will repeat the analysis after Winsorizing outliers, which will be defined as points more than 1.5 times the interquartile range below the 25^{th} or above the 75^{th} percentile of the overall distribution. No adjustment will be made to p-values or confidence intervals for multiple comparisons for the primary outcome.

*In response to a concern raised during the writing of the manuscript about possible lack of fit of the LMMs for the daily measurements, we modified the analysis plan to accommodate any detected ($P<0.1$) non-linearity in the average weight trajectory using a 3-knot cubic spline in time. If this case, the treatment effect was estimated by the fitted difference at 90 days net of any fitted between-group difference at baseline.

Our secondary outcomes will include weight, body fat, lean mass, fasting glucose, insulin, and HbA1c levels, resting metabolic rate, and total energy expenditure, assessed at the baseline and 12-week clinical visits for a subset of 46 participants. To estimate the intention to treat effect of treatment assignment on changes in these outcomes, we will use LMMs with fixed effects for treatment assignment, an indicator for the 12-week visit, and their interaction, and a random effects for participant. The treatment effect will be estimated by the interaction. In sensitivity analyses, we will repeat these analyses Winsorizing any outliers, defined as in the primary analysis. P-values and confidence intervals will be Bonferroni-corrected for 8 comparisons.

All other outcomes measured at the baseline and 12-week clinical visits will be considered exploratory and analyzed using the methods described for the secondary outcomes, without penalization for multiple comparisons.